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title

Osteopenia and osteoporosis in HIV-infected patients

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summary

Osteoporosis is a skeletal system disease and is a result of balance disorders in the process of bone rebuilding, where cell mechanisms responsible for bone resorption dominate over the mechanisms that build the bone.Osteoporosis and osteopenia is noticeable metabolic complication in HIV-infected patients. Pathogenesis of bone mass decrease is complex.

key words

address

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Osteoporosis is the most frequent skeletal system disease. According to the definition by WHO (World Health Organization), osteoporosis is a skeletal system disease that characterizes with low bone mass, microarchitecture disorders, and increased bone fragility. (1, 2). Since 2001 there has been another definition applied that was developed by NOF(National Osteoporosis Foundation) and NIH(National Institutes of Health USA), which describes osteoporosis as "a skeleton system disease that characterizes with an impaired bone endurance, which increases the risk of fracture. First of all, bone endurance reflects bone mineral density combined with bone quality".According to the two definitions, osteoporosis is diagnosed on the basis of lowered bone mineral density (BMD), which combined with increased bone fragility, increase susceptibility to fractures, and consequently exacerbated pain, disability, limited mobility, and premature death. Fractures occur due to low-energy injuries, with the most serious fracture being femoral neck fracture, which are related with a high morbidity rate and high mortality rate (3).

In osteoporosis diagnostics, the method of DXA-Dual Energy X-ray Absorptiometry is applied. The examination result gives us the absolute value of bone mineral density expressed in mass (BMD). This figure divided by the surface examined results in bone mineral density in g/cm^2(BMD). As recommended by WHO and ISCD (International Society for Clinical Densitometry), the measurement is supposed to be done: 1. in the proximal femur (the femoral neck, shaft, Ward's triangle, or greater trochanter – results for each of these spots individually or for the total hip are assumed to be standard spots in diagnosing osteoporosis and estimating fracture risk, 2. the spine (L1-L4 lumbar spine in P-A projection; the measurement should cover at least 2 vertebrae) – the spot recognized as an alternative to the proximal femur in diagnosis osteoporosis. 3. 1/3 of the radial bone- recommended when the measurement cannot be made in the proximal femur and spine (8). According to WHO, osteoporosis is diagnosed on the basis of T-score or Z-score (T-score defines the deviation from the norm for a healthy person aged 20-29; Z-score defines the deviation from the norm for the age and the same sex; the reference standard for femoral neck is BMD 0.572 g/cm^2). When the T-score value is between -1.0 to -2.5 one can talk about osteopenia; if it is below -2.5 one can talk about osteoporosis, if it is below -2.5 and coexists with osteoporotic fracture, advanced osteoporosis can be diagnosed (9, 10). Quantitative Ultrasonography (QUS) measures the attenuation and speed of sound in various parts of the skeleton, but it does not define mineral bone density and cannot be used in osteoporosis diagnostics; it can be used only to estimate the risk of fracture (9). Quantitative computer tomography (QCT) allows for three-dimensional bone examination and the actual measurement of bone density. However, due to high radiation doses, small accuracy, high costs, and little availability is it not considered a standard examination. The application of radiological examination characterizes with low sensitivity and it is usually performed in order to state or eliminate fracture.

There is a linear correlation between a fall in BMD and the risk of fracture; however, 55-70% of fractures occur in people with normal BMD (11, 12). There are other risk factors which need to be taken into consideration when making fracture prognosis. These include the following: the genetic factor (female sex, mother's family history of femoral neck fracture, Caucasian or Asian race), the demographic one (advanced age ≥ 65 years, small body mass BMI-body mass index ≤ 19 kg/m^2, previous fractures due to low energy injuries), the hormonal factor (estrogen deficit, hipogonadism), the disease one (rheumatoid arthritis, hyperthyroidism, serious organ diseases), the behavioural one (low calcium supply, sitting lifestyle, vitamin D deficiency, smoking tobacco, alcohol abuse), medication (glucocorticosteroids, anti-convulsive drugs, long-term use of heparin in big doses, big doses of methotrexate) (13, 14, 15).

Osteoporosis is a result of balance disorders in the process of bone rebuilding, where cell mechanisms responsible for bone resorption dominate over the mechanisms that build the bone (4).

A bone consists of the outer part (cortical bone) and the inner part (trabecular bone) which is filled with collagen, calcium, and other minerals. In both of these bone types there are osteoblasts and osteoclasts, i.e. cells responsible for the process of bone rebuilding (16, 17, 18). Bone rebuilding is a constant process, continuing also after bone growth has been completed. Trabecular bone is the most active in terms of metabolism as it contains large clusters of osteoblasts and osteoclasts. Osteoclasts are large multinuclear cells that develop from mother cells and are found to appear individually or in clusters. Their activation can be influenced by many factors like CSFs (Colony Stimuling Factor) – particularly M-CSF (Macrophage Colony Stimuling Factor), TNF (Tumor Necrosis Factor), RANK ligand (Receptor for Activation of Nuclear factor-kappa 2) = ODF (Osteoclast Differentiation Factor), interleukins (IL-1, IL11, IL-6, IL-17), as well as the endogenous mediator NO (Nitric Oxide). Via the system of proton pomp, osteoclasts produce acid which dissolves the crystals of hydroxyapatit in the bone leading to the exposition of the protein matrix, which is then dissolved by digestive enzymes (16). There are many enzymes related with osteoclasts that participate in this entire process (carbonic anhydrase II, cathepsins, metalloproteinases, collagenases, TRACP- tartrate resistant acid phosphatase type V). Osteoblasts develop from precursor cells that are capable of multidirectional development. Their activity is influenced by numerous growth factors including IGFs (Insulin-like Growth Factors), FGFs (Fibroblast Growth Factors), TGF-ß, BMPs (Bone Morphogenetic Proteins). Osteoblasts themselves produce many factors that perform the function of auto- and paracrine regulators of skeletal cell activity (RANK-ligand, CSFs, interleukin – 6, interleukin 11) and cell matrix proteins (procollagen, osteocalcin, osteonectin, sialoprotein, proteoglycans) that form a scaffold, which is further subject to mineralization with alkaline phosphatase enzyme (16). Produced by osteoblasts, procollagen has N-end and C-end areas, which are cleaved by some proteases in extracellural space and released there. These parts are called PICP and PINP: C-terminal propeptide of type I procollagen and N-terminal propeptide of type I collagen. Type I collagen is of spiral structure; only C- and N-terminal telopeptides are of non-spiral structure – these are CTX and NTX, i.e. C-telopeptide cross-links of type I collagen and N-telopeptide cross-links of type I collagen. Collagen networking elements include pyridinoline and deoxypyridinoline. Thus, the biochemical markers of osteogenesis include alkaline phosphatase, osteocalcin, propeptide of type I procollagen (PINP, PICP); the biochemical markers of osteolysis include tartrate resistant acid phosphatase, pyridinoline, deoxypyridinoline, telopeptide cross-links of type I collagen (CTX, NTX).

The pathogenesis of bone mass decrease in HIV patients is complex. It is influenced by and results from numerous possible factors. Bone mass decrease in HIV patients is a result of the interaction between bones' natural environment, T lymphocytes, osteoclasts, and osteoblasts. Apart from this, it is also affected by nutrition factors, hormonal

changes, deficiency in vitamin D and Ca. HIV patients are more susceptible to aseptic bone necrosis, mostly in the hip area (19). Aseptic bone necrosis of nonvascular origin has been noted (20). It can be a result of the infection itself and HAART therapy as well as some other factors which coexist with HIV infection. The impact of antiphospholipid antibodies is also possible (21). Chronic HIV infection results in a inhibited activity of T lymphocytes and an increased synthesis of proinflammatory factors, cytokines that affect bone resorption, as well as TNFα, IL-6 (22, 23), both in the system and inside the skeletal structure (24, 25, 26). Cytokines stimulate the activity of osteoclasts and reduce their apoptosis (27).

T lymphocyte clusters along with the soluble HIV-1 surface and surface glycoprotein gp120 induce RANKL expression in vitro (25). Moreover, the appearance of osteoclasts' precursors depends on peripheral mononuclear cells, which are exposed to 120 gp and induce the formation of resorpting osteoclasts. This effect is blocked by RANKL antibodies and partly inhibited by TNFα-antibodies (28); it can be reinforced by synergistic activity of glycocorticosteroids (29).Body mass defined as lowered BMI (Body Mass Index), serious body mass decrease, low fat mass, and considerable body mass variations are related to BMD fall (30, 31, 32, 33, 34).Irregularities in calcium supply and the homeostasis between vitamin D and PTH (Parathyroid hormone) are quite frequent in HIV infected patients. Lowered PTH secretion and PTH immunity result in lowered calcemy (35, 36, 37, 38, 39, 30, 40, and 41). A considerable fall in the level of 1.25 (OH) 2D in blood serum is observed in patients with the advanced disease (42, 43, 44, 45). This may be a consequence of decreased activity of 1?- hydroxylases (35, 45, and 46). Furthermore, the transition of 25-OHD to 1.25 (OH) 2D is controlled by cytochrome P450 and is inhibited by some IP in vitro (47). Sex hormones are definitely related to bone mass decrease both in ill men and women. There is a fall both in sex and adrenal hormones in men with HIV infection (45, 48), which leads to hypogonadism and hypovitaminosis D, and then to bone mass decrease (49, 50). In women with HIV infection, on the other hand, menstruation is present or not, which entails that the level of estrogens and testosterone is related to BMD (30). Menopause has a negative influence on bone mass (34). Weaker due to the regulation down, estrogens' influence on the expression of cytokines, which impact bone resorption (51, 52) and are produced by the activated T cells as well as by RANKL expression of skeletal matrix cells (53); however, due to the regulation up, they cause gene expression and synthesis for osteoprotegerin. What plays a reliable role in skeletal metabolism is the central growth hormone (GH), which could be potential remedy for people suffering from HIV and from lowered BMD (54). Histomorphometric examinations of HIV patients showed the coexistence of bone resorption and formation, yet, the mineralization rate of a new osteoid was decreased considerably. The osteocalcin level in blood serum fell considerably – respectively to the reduction of skeletal formation in bone biopsy materials and respectively to the illness gravity (55). An increase in CTX level and decrease in osteocalcin level depending on the stage and gravity of the infection were also confirmed in other research (55, 56, 44, 57).

There is a correlation between patients' taking antiretroviral medication, mainly IP (protease inhibitors), and the appearance of lipodystrophy, dyslipidemia, insulin resistance, lactic acidosis, osteopeny, and osteoporosis. This may result from the activation of pro-inflammatory cytokines, from a long period of HIV treatment, hormonal condition, body build, nutrition. In patients on IP medication a considerable increase in osteoclasts' activity was observed (58), although there was research with Ritonavir, which showed inhibited osteoclasts' formation and fall in osteoclasts' level in the resorption spot. These phenomena were dependent on the medication dose, where doses of Ritonavir toxic (non-pharmacological) inhibited osteoclastogenesis (28). In HIV patients with lowered bone mass there is increased concentration of skeletal resorption markers noted along with variable concentration of bone formation markers (56, 59, 60). The RANKL level in blood serum was on the increase in HIV patients who were subject to antiretroviral therapy (ART) as compared to those who did not undergo ART, which in turn correlated with BMD in the lumbar spine and deoxypyridinoline in urine, and it continued to be high.

The mechanisms of nucleoside reverse transcriptase inhibitors (NRTI) influencing bone mass decrease are still uncertain. The research conducted so far shows that they contribute to the activation of osteoclastogenesis depending on the dosage (zidovudine) (62) and the coexistence of lactic acidosis with reduced bone mass (63). IP influence the regulation of osteoclasts by the expression of RANK / RANKL / OPG (Osteoprotegerin). OPG is a leading factor that increases osteoclastogenesis and bone resorption (64, 65). AZT activates osteoclastogenesis in RAW 264 cells and primary precursors of osteoclasts in the presence of RANKL (66). This effect is related to an increase in tartrate resistant acid phosphatase (TRAP) and NF-κβ transcription factor. The effect depends on AZT concentration and activation of TRAP and calcitonin receptors (CTR – Calcitonin Receptor). NRTI activate T-cell cytokines and macrophages (IFN-α, IFN-β, tumor necrosis factor – TNF-α, interleukins, CD40L, GM-CSF-granulocyte-macrophage colony-stimulating, MIP-1-macrophage inflammation protein), which have an impact on osteoclasts' formation and function and released RANKL. The activated T lymphocyte produced IFN-γ, which inhibits osteoclastogenesis in vitro (67, 68, 69, 70). Mitochondria perform many important cell functions; their damage or dysfunction leads to metabolic disorders. Lactic acidosis is one of mitochondrial diseases, which is observed in patients treated with NRTI with lowered BMI. NRTI influence reverse transcriptase, and thus inhibit the virus replication; moreover, they inhibit γ-polymerases and mtDNA synthesis, which causes damage and dysfunction of mitochondria. RANKL appears in order to prevent the damage to mtDNA. RANKL expression is related to HIV infection (28, 71) and it cannot be excluded that NRTI cause an increase in RANKL, which may have a relation to the influence of NRTI on osteoclasts' mitochondria.

Osteoporosis and osteopeny is a noticeable metabolic complication in HIV patients and during their treatment. The metaanalysis of the research conducted by Brown and Qaqish shows that osteoporosis appears in 15% of HIV patients. It is three times more frequent than in the control group of people not suffering from HIV. Antiretroviral therapy makes one more vulnerable to bone mass decrease. Additionally, such factors as disease gravity, period of therapy, smoking, calcium supply, physical activity, age, and menopause or non-menopause period in women should be taken into consideration (72). In the course of osteoporosis treatment in HIV patients tests have been performed with alendronate and risendronate that proved the effectiveness of this medication (73, 74). They have little bioavailability and are extracted unchanged by kidneys, which means that they are unlikely to interact considerably with antiretroviral medication.

References

1. Consensus development conference:Diagnosis, prophylaxis and treatment of osteoporosis.AmJMed 1993,94:646-650
2. World Health Organization:Assessment of fracture risk and its application to screening for postmenopausal osteoporosis.Technical Report Series 843, Geneva 1994
3. Cumnings S., Melton L.Epidemiology and outcomes of osteoporotic fractures.Lancet 2002;359:1761-1767
4. Hunter D., Sambrook P. Bone loss Epidemiology of bone loss.Arthritis Res.2000;2:441-445
5. Black G.M. Wahner H.W. Fogelman I.:The valuation of osteoporosis:Dual Energy X-ray Absorptiometry and Ultrasound in Clinical Practice.Martin Dunilz Ltd , London 1999
6. Lorenc R.S.(red.):Diagnostyka osteoporozy 2000.Osteoforum, Warszawa 2000
7. Przedlacki J.: Porównanie półilościowej i jakościowej metody oceny czynników ryzyka złamania kości w osteoporozie. Postępowanie w osteoporozie.cz.1.Katedra i Klinika Chorób Wewnętrznych i Nefrologii. Akademia Medyczna w Warszawie. Warszawa 2005.
8. Leib ES, Lewiecki EM, Binkley N, Hamdy RC;International Society for Clinical Densitometry. Official positions of the International Society for Clinical Densitometry. J.Clin.Densitom.2004 Spring;7(1):1-6
9. Kanis J.A., Gluer C.C.:An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporosis Int.2000, 11;192-202
10. ItoM., Nishida A., Kono J.et al.:Which bone densitometry and which skeletal site are clinically useful for monitoring bone mass. Osteoporosis Int., 2003,14, 959-964
11. Siris ES, ChenYT, Abbott TA, Barrett-ConnorE, Miller PD, Wehren LE, Berger ML.:Bone mineral density thresholds for pharmacological intervention to prevent fractures.Arch Intern Med.2004 May 24;164(10):1108-12
12. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT Orwoll ES.:Hip Fracture in Women without Osteoporosis.J.Clin Endocrinol Metab.2005 May;90(5):2787-93
13. Woolf A.,Pfleger B.Burden of major musculosceletal conditions.Bull.World Health Organ.2003;81:646-656
14. Martens M.G.Risk of fracture and treatment to prevent osteoporosisrelated fracture in postmenopauzal women.A review.J.Reprod.Med.2003;48:425-434
15. Hansen L.B. and Vondracek S.F.Prevention and treatment of nonpostmenopausal osteoporosis.Am.J.Health Syst. Pharm.2004;61:2637-2656
16. Inzerillo A., Zaidi M.Osteoporosis:trends and intervention. Mt.Sinai J.Med.2002;69:220-231
17. Raisz L. Local and systemic factors in the patogenesis of osteoporosis.N.Engl.J.Med.1988;318:818-828
18. Compston J.,Rosen C Fast Facts- Osteoporosis. Wyd.3.Health Press, Oxford 2002
19. Allison G.T. et al.2003.Osteonecrosis in HIV disease:epidemiology, etiologies, and clinical management.AIDS 17:1-9
20. Keruly J.C. et al. 2001 Increasing incidence of avascular necrosis of the hip in HIV-infected patients.J.Acquir.Immune.Defic.Syndr.28:101-102
21. Belmonte M.A. et al. 1993 Avascular necrosis of bone in human immunodeficiency virus and antiphopsholipid antibodies,J.Rheumatol.20:1425-1428
22. Lahdevirta J. Maury CP Teppo AM, et al. Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. Am.J.Med.1988;85:289-291
23. Breen EC, Rezai AR, Nakajima K. et al. Infection with HIV is associated with elevated Il-6 levels and production.J Immunol. 1990;144:480-484
24. Manolagas SC, Jilka RL.Bone marrow, cytokines and bone remodeling:emerging insights into the patophysiology of osteoporosis.N Engl J Med. 1995;332:305-311
25. Roodman GD.Role of cytokines the regulation of bone resorption.Calcif Tissue Int.1993;53(Suppl):S94-S98
26. Alsina M. Guise TA. Roodman GD.Cytokine regulation of bone cell differentation.Vitam Horm 1996;52:63-98
27. Armstrong AP, Tometsko ME, Glaccum M, et al. A RANK/TRAF6-dependent signal transduction pathway is essential for osteoclast cytoskeletal organization and resorptive function.J Biol Chem 2002;277:44347-44356
28. Fakruddin JM, Laurence J. HIV envelope gp 120-mediated regulation of osteoclastogenesis via RANKL secretion and its modulation by certain HIV protease inhibitors through interferon-gamma/RANKL cross-talk.J Biol Chem 2003;278:48251-48258
29. Fakruddin JM, Laurence J.HIV-1 Vpr enhances production of receptor of activated NF-kappa ? ligand(RANKL) via potentiation of glucocorticoid receptor activity.Arch.Virol.2005;150:67-78
30. Huang JS Wilkie SJ Sullivan MP et al. Reduced bone density in androgendeficient women with acquired immune deficiency syndrome wasting.J Clin Endocrinol Metab 2001;86:3533-3539
31. Mondy K Yarasheski K Powderly WG et al. Longitudinal evolution of bone mineral density and bone markers in human immunideficiency virus-infected individuals.Clin Infect Dis 2003;36:482-490
32. Rosenthall L. Falutz J. Bone mineral changes in AIDS associated lipodystrophy(abstract) J Bone Mineral Res 2003;18(Suppl):278
33. Gold J Pocock N Li Y et al. Bone mineral density abnormalities in patients with HIV infection. J Acquir Immune Defic Syndr 2002;30:131-132
34. Yin M DobkinJ BrudneyK et al. Bone mass and mineral metabolism in HIV+ postmenopausal women.Osteoporos Int 2005;16:1345-1352
35. KuhneCA Heufelder AE Hofbauer LC Bone and mineral metabolism in human immunodeficiency virus infection J bone Miner Res 2001;16:2-9
36. Welch K Finkbeiner W Alpers CE et al. Autopsy findings in the acquiredimmune deficiency syndrome.JAMA 1984;252:1152-1159
37. Hellman P Albert J Gidlund M et al.Impaired parathyroid hormone release in human immunideficiency virus infection.AIDS Res Hum Retroviruses1994;10:391-394
38. Palestine AG Polis MA De Smet MD et al. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS(comment).Ann Intern Med. 1991;115:665-673
39. Wharton JM Coleman DL Wofsy CB et al. Trimethoprim-sulfamethoxazole or pentamidine for Pneumocystis Carinii pneumonia in the acquired immunodeficiency syndrom: a prospective randomized trial.Ann Intern Med. 1986;105:37-44
40. Brown T Ruppe M Kassner R et al. Reduced bone mineral density in HIV infected patients and its association with increased central adiposity and postload hyperglicemia.J Clin Endocrinol Metab 2004;89:1200-1206
41. Bruera D Luna N David DO et al.Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy.AIDS 2003;17:1917-1923
42. Teichmann J Stephan E Lange U et al. Osteopenia in HIV-infected women prior to highly active antiretroviral therapy. J Infect 2003;46:221-227
43. Aukrust P Haug CJ Ueland T et al. Decreased bone formative and enhanced resorptive markers in human immunodeficiency virus infection:indication of normalization of the bone -remodeling process during highly active antiretroviral therapy L Clin Endocrinol Metab 1999;84:145-150
44. Teichmann J Stephan E Discher T et al.Changes in calciotropic hormones and biochemical markers of bone metabolism in patients with human immunodeficiency virus infecion Metab Clin Exp 2000;49:1134-1139
45. Haug CJ Aukrust P Haug E et al. Severe deficiency of 1,25-dihydroxyvitaminD3 in human immunodeficiency virus infection:association with immunological hyperactivity and only minor changes in calcium homeostasis.J Clin Endocrinol Metab;1998;83:3832-3838

46. Kuehn EW Anders HJ Bogner JR et al.Hypocalcaemia in HIV infection and AIDS. J Intern Med. 1999;245:69-73
47. Cozzolino M Vidal M Arcidiacono MV et al. HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D.AIDS 2003;17:513-520
48. Christeff N Gharakhanian S Thobie N et al. Evidence for changes in adrenal and testicular steroids during HIV infection.J Acquir Immune Defic Syndr 1992;5:841-846
49. Ramayo E Gonzalez-Moreno MP Macias J et al. Relationship between osteopenia, free testosterone, and vitamin D metabolite levels in HIV-infected patients with and without HAART.AIDS Res Human Retroviruses 2005;21:915-921
50. Fairfield WP Finkelstein JS Klibanski A Grinspoon SK Osteopenia ineugonadal men with acquired immune deficiency syndrome wasting syndrome.J Clin Endocrinol Metab 2005;21:915-921
51. Manolagas SC.Role cytokines in bone resorption.Bone 1995;17(2 Suppl):63S-67S
52. Pacifici R.Estrogen, cytokines, and pathogenesis of postmenopausal osteoporosis.J Bone Mineral Res 1996;11:1043-1051
53. Eghbali-Fatourechi G Khosla S Sanyal A et al. Role of RANKL ligand in madiating increased bone resorption in early postmenopausal women.J Clin Invest 2003:111:1221-1230
54. Kotkia P Canavan B Breu J Grinspoon S Effects of growth hormone-relasing hormone on bone turnover in human immunodeficiency virus-infected men with fat accumulation.J Clin Endocrinol Metab 2005;90:2154-2160
55. Serrano S Marinoso ML Soriano JC et al. Bone remodeling in human immunodeficiency virus-1-infected patients:a histomorphometric study.Bone 1995;16:185-191
56. Teichmann J Stephan E Lange U et al. Osteopenia in HIV-infected women prior to highly active antiretroviral therapy J Infect 2003;46:221-227
57. McNurlan MA Garlick PJ Frost RA et al.Albumin synthesis and bone collagen formation in human immunodeficiency virus-positive subject:differential effects of growth hormone administration.J Clin Endocrinol Metab 1998;83:3050-3055
58. Jain RG Lenhard JM Select HIV protease inhibitors alter bone and fat metabolism ex vivo. J Biol Chem 2002;277:19247-19250
59. Fairfield WP Finkelstein JS Klibanski A et al. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome.J Clin Endocrinol Metab 2001;86:2020-20-26
60. Zamboni G Antoniazzi F Bertoldo F et al.Altered bone metabolism in children infected with human immunodeficiency virus.Acta Paediatr 2003;92:12-16
61. Konishi M Takahashi K Yoshimoto E et al.Association between osteopenia/osteoporosis and the serum RANKL in HIV-infected patients.AIDS 2005;19:1240-1241
62. Pan G Wu X Mc Kenna MA et al. AZT enhances osteoclastogenesis and bone loss.AIDS Res Hum Retroviruses 2004;20:608-620
63. Carr A Miller J Eisman JA Cooper DA.Osteopenia in HIV-infected men:association with asymptomatic lactic academia and lower weight preantiretroviral therapy.AIDS 2001;15:703-709
64. Jain,R.G.&J.M.Lenhard.2002.Select HIV protease inhibitors alter bone and fat metabolism ex vivo.J.Biol.Chem.277 :19247-19250
65. Wang, M.W.et al. 2004.The HIV protease inhibitor ritonavir blocks osteoclastogenesis and function by impairing RANKL-induced signaling.J.Clin.Invest.114:206-213
66. Pan, G. et al. 2004.AZT enhances osteoclastogenesis and bone loss.AIDS Res.Hum.Retroviruses 20:608-620
67. Takayanagi, H. et al.2000.T-cell-mediated regulation of osteoclastogenesis by signallig cross-talk between RANKL and IFN-gamma.Nature 408:600-605
68. Wei, S. et al.2002.Interleukin-4 reversibly inhibits osteoclastogenesis via inhibition of NF-kappa B and mitogen-activated protein kinase signaling.J.Biol.Chem.277:6622-6630
69. Wei,S.et al.2005.Il-1 mediates TNF-induced osteoclastogenesis.J.Clin.Invest.115:282-290
70. Wong,T.Y.&M.K.So.2001.Primary human immunodeficiency virus infection:heightened awareness needed.Hong Kong Med.J.7:205-20needed.Hong Kong Med.J.7:205-208
71. Fakruddin, J.M.&Laurence.2004.Interactions among human immunodeficiency virus (HIV)-1, interferon-gamma and receptor of activated NF-kappa B ligand(RANKL):implications for HIV pathogenesis.Clin.Exp.Immunol.137:538-545
72. T.T.Brown R.B.Qaqish, Antiretroviral therapy and the prevalence of osteopenia and osteoporoza:a meta-analytic review. AIDS 20(17):2165-2174.November 14,2006
73. Mondy K,Powderly WG,Claxton SA,et al.Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection.J.Acquir Immune Defic Syndr 2005;38:426-431
74. Dunn CJ, Goa KL.Risedronate:a review of its pharmacological properties and clinical use in resorbtive bone disease. Drugs 2001;61:685-712

title

Spirituality in coping with HIV/AIDS

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summary

This article creates a general framework for spirituality and HIV/AIDS as a chronic illness using a health care perspective. Spirituality provides an important function of helping people to find meaning and purpose in their lives. Various research findings that support the use of spirituality for coping with HIV/AIDS will be provided. Having been defined as one of the coping means with HIV/AIDS, spirituality is argued in this paper as an empowering resource in both well-being of the individuals with such a life threatening illness and their adaptation to the illness process. It has been observed in many researches held in varying research designs with various patient groups that as the functioning of spirituality in the patients with HIV/AIDS increases, depression, hopelessness and level of anxiety decrease; and adaptation, life satisfaction and quality of life proliferate. This paper argues it is extremely important that the professionals in the field of health support the patients who try to cope with especially the psychological and emotional effects of the illness process not only psycho-socially but also in forming meaning and goals about life as well as empower them spiritually.

key words

Spirituality, HIV/AIDS, coping, medical social work

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INTRODUCTION

"Death could be born only where the meaning and purpose of life, and ultimately hope is exhausted."

Health is defined in recent years as a multi-dimensional concept which foresees a complete wellbeing not only physically, psychologically, mentally and socially, but also spiritually. Within this framework, besides some philosophers, many behavioral and social science academicians define health on philosophical grounds as the wholeness and especially harmony of mind, body and spirit, in which while the spirit controls the mind the later controls the body. They even go further and describe the individual philosophically not as *"a human being who bears spiritual experiences"*, but as *"a spiritual being who bears human experiences"* [1,2]. Therefore, it is considered that the spiritual area takes place among the high priority components in forming the wellbeing of the individual.

Apparently, embracing the individual's biopsychosocial environment, spirituality has begun to be included among the scales which are used to determine the variables such as quality of life and life satisfaction in various illnesses including mental disorders [3,4,5,6].

At this point the concept of spirituality needs to be clarified. One definition of spirituality puts it as the power beyond the individual himself/herself and his/her existence. Another defines it as the personal awareness covering both the physical and the metaphysical [7]. A more comprehensive definition of Elkins *et all.* (1988) includes such components as transcendental dimension, goal and meaning of life, basic mission in life, sacredness of life, material values, altruism, and idealism, etc. [8].

Naming spirituality and the spiritual arena of the individual as a phenomenon and restricting those with certain limits is quite difficult due to the vague and complicated nature of the concept. This difficulty results from the fact that spirituality is mostly individual based, subjective, unique and mysterious [9]. Moreover, what is common in all the definitions of the concept is to perceive life as "*meaning*" and "*purpose*".

Spirituality from the health perspective is defined as the individual's intrapersonal and interpersonal connectedness and his/her connectedness with transcendental purposes [10,11,12]; and defining the term in this way also includes the dimensions of spirituality. Built upon a three-dimensional scope, spirituality explains the very meaning of the individual's existence. Therefore, the point at which the individual grasps the meaning and purpose of life is his/her spiritual arena which may be either the subjective and esoteric relationship with God or a Higher Power, or a relationship of value and belief with nature, arts, music, family, and social environment, etc. [13]. Undoubtedly, aggregate of all those may be seen as the components which help the individual give meaning to his/her own life.

To put these dimensions into more concrete terms within the context of HIV/AIDS patients, intrapersonal connectedness is related to the individual's feelings on their own self. While the individual's love, acceptance and awareness of his/her own self increase, his/her spiritual wellbeing advances. The individual's following states of mind address the power of his/her connectedness with the self: (*i) I feel myself peaceful, (ii) I have reasons to live, (iii) I have certain goals in my life,* and *(iv) I am satisfied with life.*

Interpersonal connectedness refers primarily to the individual's family, and social and cultural environment including also peer groups and health professionals. Tolerant attitudes towards and strong links with the views, values and beliefs of these environmental factors strengthen the wellbeing of the individual in his/her spiritual area.

Transcendental connectedness, on the other hand, implies practices towards the believed Higher Power. These practices may appear as pray for *"getting closer to the superior power"* and reaching peace, religious rituals as worshipping, and/or inclination towards some spiritual endeavor with a strong bond of love (such as nature, arts, music, stars, and meditation, etc.).

The notion of connectedness is often encountered in the scientific literature on spirituality. Connectedness helps one set up links with sources stronger than him/her [14]. Connectedness within chronic illnesses in general and HIV/AIDS in particular creates opportunities for the individuals to get motivated and strengthened in coping with the illness. The search for meaning, on the other hand, is to form a goal and meaning about life within the context of the illness [14,15]. Attributing meaning to the illness process is also a quite effective coping mean for the individual; providing him/her with the possibility of a close and profound relationship with his/her own self, the Higher Power, and the environment, it helps him/her value life and construct an intellectual control on what is happening.

Connectedness and the search for meaning make up the fundamental components of spirituality in the HIV/AIDS context. What is at stake in this point is the fact that the individual both inclines towards either his/her deeps or a sacred power through the belief systems, and involves in a closer communication with his/her environment. Such tendencies facilitate the control of the illness for the individuals who are confronted with a dangerous life event as HIV/AIDS.

Elkins *et all.* (1988) developed a conceptual design on spirituality and included four assumptions in it: firstly, spirituality is a human phenomenon and located in every person potentially. Secondly, spirituality could be defined and explained by phenomenological approaches. Thirdly, spirituality is a human experience which includes values, attitudes, perspectives, beliefs and feelings. Finally, spirituality is not the same as religion [8]. In this phase, we need to clarify the structural differences between religion and spirituality.

RELATIONSHIP BETWEEN RELIGION AND SPIRITUALITY

Religion and spirituality is usually a matter of heated discussion. The literature often witnesses interchangeable uses of the two. The reason why spirituality had not long been included among the basics of the health paradigm (including physical, psychological, mental, cultural, and social aspects) is the fact that it is seen as analogous to theology's main subject, religion. However it should be noted that there is a conceptual difference between spirituality and religion, and the former is a broader concept which embraces the later [16,17].

Religion implies an institutional and complex structure comprised of beliefs, rules, rituals, and practices. It is essentially a moral institution and what lies in its essence is the faith in and submission to God who has the power to create. In addition, while religious beliefs and practices are based on sacredness to a greatest extent, spirituality focuses on the image of self [18].

Having a composition which also includes religion, spirituality refers to the entire individual experiences, thoughts and feelings. In this respect, it appears in all societies and different belief systems, and bears a universal characteristic. Nevertheless, it is possible to find some elements of religion in spirituality, and vice versa, which obviously addresses the fact that the two complete each other. Spirituality includes subjective experiences, thoughts and feelings on the mystery (and metaphysics) in human life. It is concerned with the individual's search for meaning and emotions about the dealings around him/her. Existentially speaking, spirituality both explains any life experience of the individual, and implies his/her search for and subjective relationship with God or higher power [19].

Having a quality beyond any religious belonging, spirituality includes even nonbelievers, and serves for the individual to attribute meaning to and set goals for life [20]. On the other hand, should spirituality have been defined as restricted and/or analogous to the faith in God or religion, it would not have been possible to witness the "*spiritual*" support of atheists, agnostics, humanists, and hedonists in forming their coping strategies [21]. Therefore, spirituality embraces all believers and nonbelievers.

Some spiritual enterprise include leisure activities in nature and strengthening of ties with the beloved, and lays stress on the individual's feelings of compassion, mercy, love, and altruism [22]. Another aspect of spirituality is its ability to explain the suffering and challenging situation via the individual's belief, and reach the conviction that it is ultimately not harmful [23,24]. At this point, suffering is considered as a valuable part of human life and real as much as joy, and happiness and pleasure are believed to be the gifts of physical and psychological pains.

In the last analysis, the following joint discourse of three celestial religions of the earth – Judaism, Christianity and Islam – as well as Buddhism and even Hinduism is extremely effective in re-explaining life and setting a spiritual wholeness by establishing relief, adaptation and inner peace in cases of HIV/AIDS and many threatening chronic illnesses: *"human life is aggregate of sorrow, pain, challenges as well as gladness, happiness and peace."*

HIV/AIDS AS A CHRONIC ILLNESS

Previously perceived as a fatal disease, HIV/AIDS has been included in the scope of chronic illnesses thanks to availability of protease inhibitors and the powerful combination of antiretroviral therapies [25]. Hence, the illnesses such as diabetes mellitus, cancer and HIV/AIDS, which create vital threats for individuals, require long run observation and protection, cause pathological transformations in physical appearance and physiological structure, and cannot be thoroughly cured but managed are by now classified within chronic illnesses. These illnesses profoundly influence the basic functions of the individual's life, and due to their unpredictable nature, inflame strong psychological, physical, sexual, social and economic pressures [26]. Having been confronted with physical and functional losses because of the illness, the individuals start evaluating their lives through a brand new perspective.

Besides, HIV/AIDS and other chronic illnesses may make the individual depend on others by impairing some of his/her functions, and this reveals an anxiety for the loss of self-control on life. Patients experience a fear of losing their economic independency and refrain from being a burden on the shoulders of their families [27]. They often suffer several psychological problems, too. Besides the pain of the illness itself, they face with some stressors as the anxiety of uncertainty and the change in the body image. Naturally, majority of these illnesses cannot be treated, but only managed. Such stressors cause a change in the patients' wellbeing and elicit an existential search for meaning and purpose which appears out in the form of the question, *"what is the meaning and purpose of life for me?"* [12,17].

Confronting a life threatening chronic illness whose treatment is not explored yet is perhaps the most distressful life experience. Researches have shown that individuals with HIV/AIDS suffer serious psychiatric disorders as well as various biological and psychosocial problems. Despite developments in antiretroviral treatments; mood, anxiety and substance abuse disorders in the patients with HIV/AIDS appear often among psychiatric disorders [28]. Furthermore, the stressors linked with the nature of the illness rigorously influence patients. Illness related stressors may include cognitive and motor decline, hospitalizations, invasive treatments, pain, fatigue, loss of mobility, sexual dysfunction and disinterest, body disfigurement, numerous unpleasant side effects from complicated medication regimens, financial burden, and the stress that accompanies facing one's own mortality [29].

Great majority of the patients who are hospitalized after a certain diagnosis experience an intense anxiety. This is a fear against their unknown and vague future caused by the illness. Furthermore, their existence in all senses is under threat [30,31,32]. This state pessimistically accelerates the progress of the illness.

Furthermore, HIV/AIDS greatly impacts populations that may already experience social stigma and discrimination [33]. Beyond the likelihood of facing multiple stigmatized identities due to race, gender, sexual orientation, and disability, many patients infected with HIV live in urban environments and may concurrently experience the stressors of poverty, unemployment, and exposure to violence and crime [29].

According to Sidell (1997), for an individual who suffers a chronic illness such as HIV/AIDS, the ultimate goal is to adapt to it, which is perhaps the most effective of all the coping struggles. On the other hand, the process of adaptation is quite complicated and covers multi-dimensional variables because every individual is influenced by his/her illness at varying levels [34]. However, universally speaking, what play an important role throughout the coping process are the support of the socio-cultural environment in the context of family and society as well as re-explaining the illness and the individual's self perception and evaluation.

It is observed after the diagnosis that some phases of general quality are achieved in the process of adaptation. The first phase is crisis which may also be described as the phase of loss. "*Loss*" means the loss of capacity, some functions, economic resources, and quality of life [35,36]. The second phase of the adaptation process comprises of the individual's confrontation with depression and emotional turmoil. Besides depression, fear, disappointment and anger are among the most intense feelings. The next phase addresses some changes in life style, everyday activities, and nourishment habits [35]. These changes indicate the fact that the illness is well managed and a process of adaptation has started. In the last phase, individuals are involved in a struggle for keeping control of their lives, and a process of empowerment starts for the individuals with HIV/AIDS [37]. Empowerment may become possible either via relationship with the environment through social support, or

with God or another Higher Power which is attributed sacredness through spiritual links.

Role of spirituality in coping with Hiv/Aids

In a longitudinal research by Szaflarski, *et all.* (2006) direct or indirect effects of spirituality on the perceptions of living of 450 patients with HIV/AIDS were examined. The research in which extensive demographic data were collected and various instruments of measurement were used revealed that having learned that they carried HIV virus, one third of the participants first experienced a deep anxiety against this vital threat, then started adapting to this pressing life event by changing their style of behavior and thinking as the acceptance and especially spiritual inclinations increased. It was determined that re-explaining life, forming goals, and keeping hope play important roles in realizing this [38]. Therefore, when the individual confronts with intensive emotional distress, somatic illness or death, the spiritual dimension appears out as a coping strategy. In another research which is qualitatively designed by Pierson, Randall-Curtis and Patrick (2002) with 35 advanced AIDS patients, spirituality and various spiritual rituals were highlighted as a very important dimension [39]. Still another research consolidated the fact that greater spiritual or religious faith follows the diagnosis of HIV/AIDS [40].

Coping is defined as the prevailing cognitive and behavioral endeavor to meet certain external and/or internal demands caused by mostly psychological and emotional pressures [41]. It is possible to classify the coping behaviors and attitudes into two, namely, the solution oriented and emotionally motivated. The former constitutes the coping behaviors and attitudes on the main source of the problem and the later constitutes the coping attitudes on the emotional effects of the main source [41]. In other words, coping attitudes are classified as active and passive. The active ones comprise of behavioral or psychological reactions aimed at either changing the stressor itself or demolishing it; and the passive ones include the acts which help avoiding the stressors. In coping with HIV/AIDS, as demanding direct assistance from the environment means active coping, adaptation to the physical and psychological change refers to the emotionally motivated coping.

Despite the fact that research literature covers a vast number of works on coping, majority of all are illness or stress based. The work on the role of religion and spirituality in coping with the illness, on the other hand, seems limited [42].

Two assumptions have quite dominantly triggered the neglect of spiritual dimension in researches. First is to argue that spirituality cannot be worked through scientific glasses. The second is the common belief that spirituality cannot be studied in a scientific frame because it is the very subject of theology. Here, the corner stone of the discussion is how to do the measurement [43]. Nevertheless, spirituality has been welcomed in scientific realm especially since the 1970's following the changes in social science paradigm, the increase in the inclination of drawing a picture of the whole instead of generalizing the results, and assignment of the individuals not as the object, but as the subject of the research.

A considerable number of both qualitative and quantitative research with various patient groups show that an increase in the functioning of spirituality in the individuals with HIV/AIDS decreases depression, hopelessness, level of anxiety, suicidal thoughts, and expectation for a quick death, and stimulates psychological functions, adaptation to the illness process, life satisfaction, and quality of life [25,38,44,45,46,47]. Moreover, even the chronic patients who proclaim the negation of any higher power may raise a hope for survival via coping with the illness in his/her subconscious, and an expectation for a divine miracle.

In a quantitative research held on 201 patients with various chronic illnesses by Rowe and Allen (2004), the relationship between spirituality and coping was analyzed. A positive correlation was identified between the increase in the intrapersonal, interpersonal and transcendental connectedness of the patients and their psychological wellbeing and functions [17]. In another quantitative research by Cotton, *et all.* (2006), 450 patients with HIV/AIDS were followed 18 months and implemented various scales periodically. It was identified as a result that three-fourth of all thought "HIV/AIDS would strengthen their belief." It was observed that majority of the participants experienced an increase in their hope for life, self-esteem and life satisfaction owing to spiritual coping strategies. In addition, rather low use of alcohol and substance was noticed among them. Finally, a negative correlation was found between the patients' spiritual functions and their levels of depression and hopelessness [44]. Sowell *et all.* (1997) carried a qualitative research with 27 women who were diagnosed as HIV/AIDS. It was affirmed in this research which is based on focus group interviews that the connectedness with primarily God or a Higher Power and their relatives is quite efficient in coping with the psychological effects of the illness, and by doing so, they re-explain their lives. Furthermore, it was also asserted that spiritual arenas of the patients are a quite useful and strong resource in protecting against social stigmas stemming from the nature of their illness and developing goals for future [45]. Therefore, it should be noted that spirituality exists in all patients regardless of the type of illness, the population group to be influenced, ethnicity, or religious orientation. All these studies prove that spirituality is a quite efficient instrument in coping with especially the psychological and emotional effects of HIV/AIDS.

Spiritual acts contain tolerant and pardoning attitudes, religious practices (worship, pray, etc.), and being bounded to primary relatives, other environmental actors, and every single living organism. These are quite strong coping resources for patients with chronic illnesses. In this sense, it is of assistance that physicians, nurses, social workers, psychologists, and other health professionals support patients in establishing stronger ties with these empowering sources.

Hafen *et all.* (1996) argue that threatening states of chronic illnesses such as HIV/AIDS provide a natural effect for the individual in re-interpreting his/her life and so experiencing changes in his/her spiritual arena [48]. On the other hand, individual reactions may differ in cases of crisis; the patient may not cooperate a harmony of mind, body and spirit, and achieve a positive development [49]. In this regard, it is mandatory for re-establishing the spiritual ties that the patients feel as if they keep control of their own lives instead of submitting to the illness process, which is only possible through spiritual development.

Hall (1998) explained the indicators of spiritual development. Individuals may devote themselves to God or Higher Power; and they may involve in intensive communication and relation with the environment. Consequently, individuals may form structural changes in their lives and

re-organize their personal values by capturing meaning and purpose in their illnesses [46].

Individuals may get tied up more with their religions which they think as a source of hope and power for the purpose of finding help in a chronic illness case even though they do not attribute much significance to it in their lives. Such a process was encountered in Ironson and the others' longitudinal research (2006) on 100 patients with HIV/AIDS. This four year research revealed that the participants worshipped more after the diagnosis in order to get support of the belief in God [47]. Wulff (1997) describes the reasons behind the increasing inclination in religious practices, rituals and worshipping in two dimensions: communicating with a supra-natural power and setting up a personal relief and internal peace by this communication. Therefore, a reasonable form of coping with the illness will appear as a possibility [50]. In addition, the ones who do not believe may meet their spiritual needs by concentrating on their selves and inclining towards nature, arts, music, and their close relationships. To put it into more concrete terms, what comes to the fore is to hang more on to life and get satisfied more.

Conclusions

Some theorists conceptualize spirituality as an aspect to be measured in three dimensions: practices, beliefs and life experiences [43]. Practice refers to the observable behaviors such as praying, fasting, worshipping, and meditation, etc. Beliefs are the constructs in the transcendental dimension beyond intellectual knowledge and senses changing from culture to culture. Life experiences, on the other hand, address to the field which is the most difficult to measure and assumed sacredness to the greatest extent. In this scope, regardless of being religiously based or not, spirituality could possibly be explored in every system of thought or incidence.

Coping spiritually with HIV/AIDS has a universal worth for all humanity regardless of any religious criterion. In this sense, spirituality exists neither only in synagogue, church, mosque, and temple, nor in stars, music, dance, beauty of nature and any love relationship, but every single sphere of ordinary life.

In the final analysis, confronting with HIV/AIDS whose treatment is not completely known yet, but could only be managed keeps all individuals regardless of belonging to any one religion under strain by a feeling of losing the control in their lives. In this point, stimulating spiritual coping strategies help the individual empower himself/herself and form a personal wholeness by combining "*biopsychosocial-spiritual*" perspectives.

Therefore, being an indispensable part of one's identity and world view, spirituality gives inspiring and empowering answers to the following existential questions for the individuals with life threatening illnesses such as HIV/AIDS: *"What is the meaning of life for me?", "what is my purpose in life?"*, etc. Researches focused directly on the spiritual area and conducted on patients from different age groups with quite various illness types, mostly with the ones with HIV/AIDS show that spirituality is effective in perception of life as worth living.

While the professionals in the health field know the ultimate goals on how to improve the wellbeing of the individuals with HIV/AIDS intellectually, physically, psychologically, socially, culturally, and spiritually, the spiritual dimension among these is mostly neglected. Hence, spirituality needs to be re-built by using a scientific perspective without being restricted only by theological area, and become a proper instrument to be used effectively in professional implementation of the professionals in the health field. In order to realize this, it will be of great use to notice the support patients receive from the spiritual area in coping with the psychological and emotional effects of the illness, and including spirituality to the empowering process besides family and friends, etc.

References

1. Watson J. Human Science and Human Care. New York: National League for Nursing; 1988.
2. Kelly J. Spirituality as a Coping Mechanism. Dimensions of Critical Care Nursing 2004; 23(4):162-8.
3. Molzahn AE. Spirituality in Later Life: Effect on Quality of Life. J Gerontological Nursing 2007; 33(1):32-9.
4. Mohr S, Brandt P, Borras L, Gilliéron C, Huguelet P. Toward and Integration of Spirituality and Religiousness into the Psychosocial Dimension of Schizophrenia. The American J Psychiatry 2006; 163(11):1952-9.
5. Krupski TL, Kwan L, Fink A, Sonn GA, Maliksi S, Litwin MS. Spirituality Influences Health Related Quality of Life in Men with Prostate Cancer. Psycho-Oncology 2006; 15:121-131.
6. Corrigan P, McCorkle B, Schell B, Kidder K. Religion and Spirituality in the Lives of People with Serious Mental Illness. Community Mental Health J 2003; 39(6):487-93.
7. King M, Speck P, Thomas A. Spiritual and Religious Beliefs in Acute Illness-Is This a Feasible Area for Study. Social Science and Medicine 1994; 38(4):631-6.
8. Elkins DN, Hedstrom LJ, Hughes LL, Leaf JA, Saunders C. Toward a Humanistic-Phenomenological Spirituality: Definition, Description, and Measurement. J Humanistic Psychology 1988; 28(4):5-18.
9. McSherry W. A Descriptive Survey of Nurses' Perceptions of Spirituality Care. Yorkshire (UK): UMI Pub; 1997.
10. Hunglemann J, Kenkel-Rossi E, Klassen L, Stollenwerk R. Focusing on Spiritual Well-being: Harmonious Interconnectedness of Mind, Body, Spirit: Use of The JAREL Well-being Scale. Geriatric Nursing 1996; 17(6):262-6.
11. Burns P. Elements of Spirituality and Watson's Theory of Transpersonal Caring: Expansion of Focus. In: Chinn PL, editor. Anthology in Caring. New York: National League for Nursing; 1991. p. 141-53.
12. O'Neill DP, Kenny OE. Spirituality and Chronic Illness. The Journal of Nursing Scholarship 1998; 30(3):275-80.
13. Puchalski C, Romer AL. Taking a Spiritual History Allows Clinicians to Understand Patients More Fully. Journal of Palliative Medicine 2000; 3:129–38.
14. Coyle J. Spirituality and Health: Towards a Framework for Exploring the Relationship Between Spirituality and Health. Journal of Advanced Nursing 2002; 37(6):589-97.
15. Baldacchino D, Draper P. Spiritual Coping Strategies: A Review of the Nursing Research Literature. Journal of Advanced Nursing 2001; 34(6):833-41.
16. George LK, Larson DB, Koenig HG, McCullough ME. Spirituality and Health: What We Know, What We Need to Know. Journal of Social and Clinical Psychology 2000; 19:102-16.
17. Rowe MM, Allen RG. Spirituality as a Means of Coping. American Journal of Health Studies 2004; 19(1):62-7.
18. Rumbold B. Caring for the Spirit: Lessons from Working with the Dying. Medical Journal of Australia 2003; 179(6):11-3.
19. Bradshaw A. The Spiritual Dimension of Hospice: The Secularization of an Ideal. Social Science and Medicine 1996; 43:409-19.
20. Narayanasamy B. Spiritual Care: a Resource Guide. Guildford: Quay Publishing; 1991.
21. Burnard P. The spiritual Needs of Atheists and Agnostics. Professional Nurse 1988; 4:130-2.

22. Reed PG. An Emerging Paradigm for the Investigation of Spirituality in Nursing. Research in Nursing & Health 1992; 15:349-57.
23. Tarakeshwar N, Hansen N, Kochman A, Sikkema KJ. Gender, ethnicity and spiritual coping among bereaved HIV-positive individuals. Mental Health, Religion & Culture 2005; 8(2):109-25.
24. Tarakeshwar N, Khan N, Sikkema KJ. A Relationship-Based Framework of Spirituality for Individuals with HIV. AIDS and Behavior 2006;10(1):59-70.
25. Friedland GH, Williams A. Attaining Higher Goals in HIV Treatment: The Central Importance of Adherence. HIV/AIDS 1999;61-72.
26. Duyan V, Yıldırım G. Life after HIV/AIDS. HIV & AIDS Review 2004; 3(2):48–55.
27. Schafer KM. Women Living in Paradox: Loss and Discovery in Chronic Illness. Holistic Nursing Practice 1995; 9(3):63-74.
28. Goldenberg D, Boyle BA. HIV and psychiatry: Part 1. The HIV/AIDS Reader 2000; 10(1):11-5.
29. Kalichman, SC. Understanding HIV/AIDS Advances in Research and Treatment. Washington DC: American Psychological Association; 1998.
30. Pargament KI, McCarthy S, Shah P *et. all.* Religion and HIV: A Review of the Literature and Clinical Implications. Southern Medical Journal 2004; 97(12):1201-9
31. Bowman GS, Webster RA, Thompson DR. The Reactions of 40 Patients Unexpectedly Admitted to Hospital. Journal of Clinical Nursing 1992; 1:335-8.
32. Shuldham GM, Cunningham G, Hiscock M, Luscombe P. Assessment of Anxiety in Hospital Patients. Journal of Advanced Nursing 1995; 22:87-93.
33. Duyan V. HIV/AIDS Related Stigmatization and Social Support. Health and Society 2001; 11(1):3–11.
34. Sidell NL. Adult Adjustment to Chronic Illness: A Review of the Literature. Health and Social Work 1997; 22:5-11.
35. Handron DS. Cope: Early Psychosocial Intervention for Chronic Illness. Nurse Practitioner 1995; 20(5):6-13.
36. Michael SR. Integrating Chronic Illness into One's Life: A Phenomenological Inquiry. Journal of Holistic Nursing 1996; 14(3):251-67.
37. İl S. An Empowering Approach for Individuals with HIV/AIDS. HIV & AIDS Review 2005; 4(4):48–52.
38. Szafklarski M, Ritchey N, Leonard AC *et. all.* Modeling the Effects of Spirituality/Religion on Patients' Perceptions of Living with HIV/AIDS. J Gen Int Med 2006; 21(5):28-38.
39. Pierson CM, Randall-Curtis J, Patrick DL, A good death: A qualitative study of patients with advanced AIDS. AIDS Care 2002;14(5):587-98.
40. WHOQOL HIV Group. WHOQOL-HIV for quality of life assessment among people living with HIV and AIDS: results from the field test. AIDS Care 2004; 16(7):882-9.
41. Lazarus RS. Coping Theory and Research: Past, Present and Future. Psychosomatic Medicine 1993; 55:234-47.
42. Tix AP, Fraser PA. The Use of Religious Coping during Stressful Life Events: Main Effects, Moderation, and Meditation. Journal of Consulting and Clinical Psychology 1998; 66:411-22.
43. Miller WR, Thoresen CE. Spirituality, Religion, and Health. American Psychologist 2003; 58:24-35.
44. Cotton S, Puchalski CM, Sherman SN *et. all*. Spirituality and Religion in Patients with HIV/AIDS. J Gen Int Med 2006; 21(5):5-13.
45. Sowell RL, Moneyham L, Guillory J, Seals BB, Cohen L, Demi A. Self-care Activities of Women Infected with Human Immunodeficiency Virus. Holistic Nursing Practice 1997; 11(2):18-26.
46. Hall BA. Patterns of Spirituality in Persons with Advanced HIV Disease. Research in Nursing and Health 1998; 21:143-53.
47. Ironson G, Stuetzle R, Fletcher MA. An Increase in Religiousness/Spirituality Occurs After HIV Diagnosis and Predicts Slower Disease Progression over 4 Years in People with HIV. J Gen Int Med 2006; 21(5):62-8.
48. Hafen BQ, Kauen KJ, Frandsen KJ, Smith L. The Healing Power of Spirituality. Spirituality and Health 1996; 4:377-99.
49. Soeken KL, Carson VJ. Responding to the Spiritual Needs of the Chronically Ill. Nursing Clinics of North America 1987; 22:603-9.
50. Wulff DM. Psychology of Religion. New York: John Wiley and Sons Publishing; 1997.

title

Exposure to SIVmd-2 in Southern Cameroon: Public Health Implications

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summary

Compelling evidence appeared in 2002 of human exposure to a plethora of primate lentiviruses through hunting, handling of bushmeat and/or animals kept as pets in Cameroon. To determine SIV prevalence in pet animals, analysis of 28 sera of nonhuman primates revealed no SIV infection in greater spot nosed monkey (0/5) or chimpanzee (0/10), and a prevalence rate of 23.1% (3/13) in mandrills kept as household pets in southern Cameroon. Phylogenetical analysis based on pol-integrase (IN) region and mitochondrial (mt) cytochrome b gene showed that the newly found SIVs from Mandrillus sphinx (SIVmndCM-202, SIVmndCM-211 and SIVmndCM-218) clustered significantly with SIVmnd-2. Questionnaire data were also collected to assess whether owners had experienced bites, scratches or exposure to blood and/or body fluid. Risk to human health from cross-species transmission of the newly identified SIVmnd-2 to infect humans remains unknown.

key words

address

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Chimpanzees (*Pan troglodytes troglodytes*) are recognized as the reservoir of simian immunodeficiency viruses (SIVcpzPtt) that have been introduced into humans at least three times, resulting in human immunodeficiency virus type 1 (HIV-1) groups M, O and N (a third HIV-1 lineage). [1-2] Van Heuverswyn et al. reported the discovery of HIV-1 group-O like viruses in wild gorillas. [3] The cross-species transmission of SIVcpz is now thought to have occurred through humans' being exposed to the blood of chimpanzees infected with SIVcpz during hunting and butchering of non-human primates in Central Africa early in the 20th century. [3-6] Care for captive nonhuman primates has lead to the transmission of a range of infections, including simian foamy virus (SFV) and herpesvirus B (HVB), primate malaria and tuberculosis. [4] Such behaviors can facilitate transmission of microorganisms from nonhuman primates to humans. Finally, a case of retrovirus transmission from mandrills to humans has already been documented. Simian T-cell lymphotrophic virus type 1 (STLV-1) from *M. sphinx* has been described as the simian counterpart of human T-cell lymphotrophic virus type 1 (HTLV-1) subtype D [7-8]. Moreover, a close molecular and phylogenetic relationship has been reported between STLV-1 subtype D from mandrills in Gabon and HTLV-1 strains obtained from Pygmies living in Cameroon and the Central African Republic and from a healthy non-Pygmy carrier in Gabon. To assess the potential risk of zoonotic transmission of monkey-possessing SIVs to humans, we conducted a serological and genetical survey among monkeys that were kept as household pets in southern Cameroon.

Materials and Methods

Blood samples were collected from 28 juvenile/infant nonhuman primates (NHPs) kept as household pets in rural and urban areas of Southern part of Cameroon (Figure 1.A). The plasma obtained from NHP was screened for HIV antibodies by a microparticle enzyme immunoassay kit (AxSYM HIV1/2; Dianabot, Tokyo, Japan) and particle agglutination assay (Serodia HIV-1 and HIV-2; Fujerebio, Tokyo, Japan). [5-6] All reactive specimens were confirmed by western blot (WB) (New Lavblot HIV-1 and HIV-2, Sanofi Diagnostic Pasteur, Marnes-la-Coquette, France). DNA was extracted from whole blood (Qiagen, Hilden, Germany) and a part of the *pol* sequences covering the integrase gene was amplified by nested polymerase chain reaction (PCR) using the primers, unipol 5 (5'-TGGGTACCAGCACACAAAGGAATAGGAGGAAA-3')/unipol 6 (5'-CCACAGCTGATCTCTGGCCTTCTCTGTAATAGACC-3'), in the first round; and unipol1 (5'-AGTGGATTCATAGAAAGCAGAAGT-3')/unipol 2 (5'-CCCCTATTCCTTCCCCTTCTTTTAAAA-3'), in the second round. Amplification for the *pol* region was done at 45°C for 30s for and 72°C for 1 min; with a final extension of 72°C for 10 min. To confirm the species of the SIV-infected monkeys identified in this study, we amplified and sequenced the 424 base pair (bp) fragment of mitochondrial (mt) cytochrome b gene, which can be used to distinguish subspecies of old-world primates. [6] The fragment (corresponding to nucleotides [nt] 14725-15148 of human mitochondrial DNA) was amplified in the DNA extracted from peripheral blood mononuclear cells of the SIV-positive monkeys, using Qiagen DNA extraction kit (Qiagen, Hilden, Germany). [6] Neighbor-joining phylogenetic trees including reference *pol* sequences and appropriate reference sequences for mtDNA were constructed using Clustal W then drawn using Treeview PPC version 1.6.6 (Institute of Biochemical and Life Sciences, Scotland, UK), (Figure 1.B and 1.C). Bootstrap resampling (1,000 data sets) of multiple alignments was performed to test the statistical robustness of the trees. Kimura-2 parameter was calculated with the DNADIST program in the PHYLIP package program [9-10]

Accession numbers

The DNA sequences of SIVmnd-2 and mitochondrial cytochrome b DNA determined as part of this study have been submitted to GenBank (accession numbers to be available soon).

Figure 1A. Locations of pet animals in southern and central Cameroon. Study sites with marked with a filled square indicate areas where SIVmnd-2 were isolated

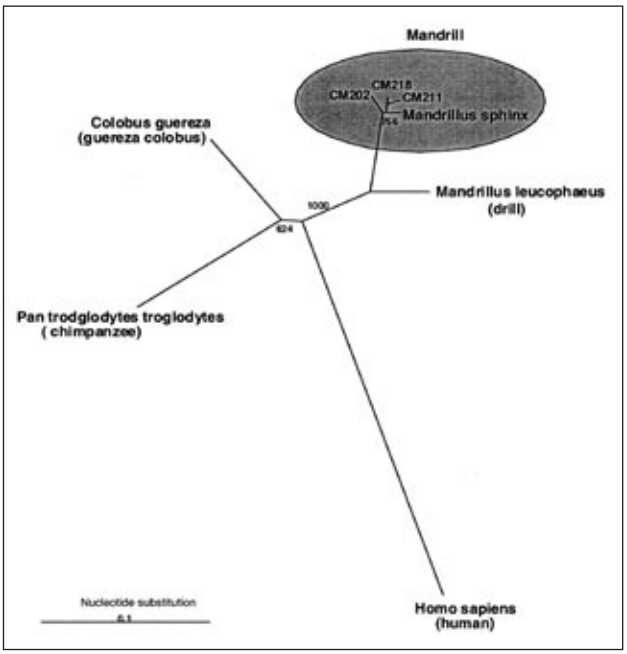

Figure 1C. Unrooted tree of the 424 base pair (bp) fragment of mitochondrial (mt) cytochrome b gene, which can be used to distinguish subspecies of old-world primates

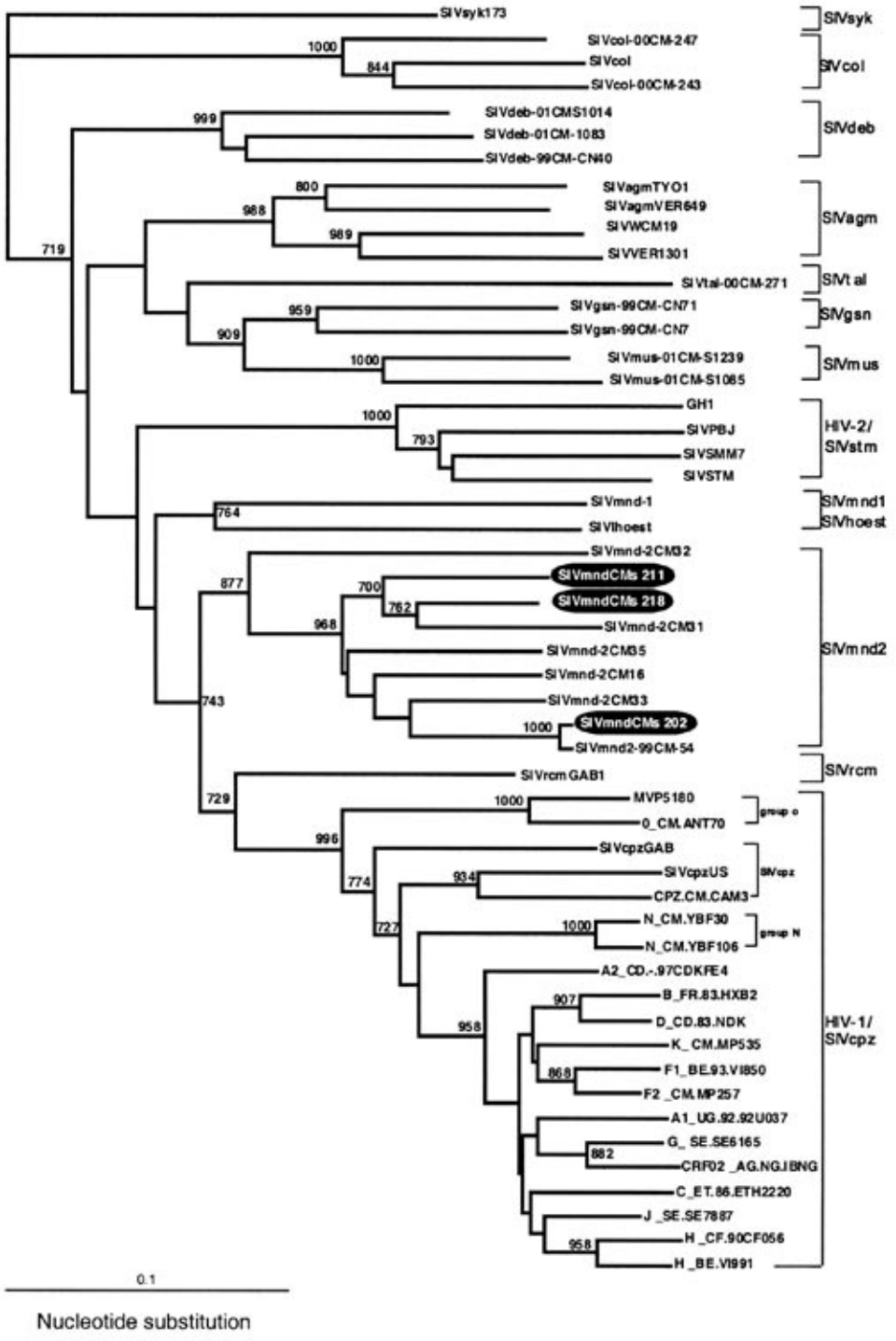

Figure 1B. Phylogenetic tree of pol sequences from three SIVmnd-2 isolates (SIVmndCM-202, SIVmndCM-211 and SIVmndCM-218). The bootstrap value at each node represents the number among 1000 bootstrap replicates that support the branching order. Bootstrap resampling of 70% or higher is shown. Brackets on the right represent the major group M subtypes

Results and Discussion

Most primates kept as household pets we identified were seen in a southern region of Cameroon (Figure 1.A). Table 1 shows the results of a serological survey of pet juvenile and infant NHPs according to species. Since commercially available HIV screening assays contain only a limited number of antigens, we used WB as a confirmatory assay. Analysis of 28 NHPs sera found no SIV infection in *Cercopithecus nictitans* (0/5, 0%), an *Pan troglodytes troglodytes* (0/10, 0%), and a prevalence rate of (3/13, 23.1%) for *Mandrillus sphinx* (Table 1). PCR amplification of short fragment of *pol*-(integrase) was successful in all sero-reactive samples. Our findings confirm a high prevalence of SIVmnd-2 infection in mandrills as described by Peeters et al. [11] in 7/20 (35%) of pet animals in southern Cameroon. The mandrill is a large semi-terrestrial primate belonging to the *Papionini* tribe, living in the tropical rain forests of Cameroon and Gabon. [9-10] Behavioral data generated by Wolfe et al. [4] from a study conducted among 3,971 persons in seventeen village sites in southern Cameroon indi-

cated that monkeys were kept more frequently than other types of wild animals. Of people sampled across all sites, 0.6% kept gorillas, 1.5% chimpanzees, 9.9% monkeys, and 1.8% rodents. [4] In our study most of the pets were still juveniles or infants at the time of sampling, and 17.8% were greater spot-nosed monkeys, 35.7% chimpanzees and 46.4% mandrills. Previous studies also reported a high proportion of greater spot-nosed monkeys (44/215, 20.5%), mustached guenons (29/215, 13.5%), olive baboons (22/215, 10.2%) and mandrills (20/215, 9.3%) domesticated monkeys in southern Cameroon. [11-12] During the 20th century, firearms increased the efficiency and frequency of hunting. Both subsistence and commercial hunting with wire snares and firearms are widespread activities throughout the forests of central Africa. [4] Most pet monkeys are acquired at very young age, often when their parents are killed by hunters. Because pets are usually young, the prevalence of chronic diseases in this population may be less than that among adult primates to which hunters and butchers are exposed. Nevertheless, because of the potential for regular contact with pet animals, even a low frequency of infections among pets may be important.

As SIVsm was able to jump to the human population, the possibility that SIVmnd-infected mandrills could also represent a reservoir posing a risk for humans cannot be excluded. Thus, further study will be necessaries to clarify if SIVmnd-2 is capable of zoonotic transmission, and if interventions will be necessary to prevent the introduction of a SIV into humans and the appearance of new "HIV" in central Africa.

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References

1. Hahn BH, Shaw GM, De Cock KM, and Sharp PM: AIDS as zoonosis: scientific and public health implications. Science 2000; 287:607-614.
2. Keele BF, Van Heuverswyn F, Li Y et al. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. Science 2006; 313:523-6.
3. Van Heuverswyn F, Li Y, Neel C et al. SIV infection in wild gorillas. Nature 2006; 444:164.
4. Wolfe ND, Heneine W, Carr JK et al. Emergence of unique primate T-lymphotropic viruses among central African bush meat hunters. PNAS 2005; 102:7994-7999.
5. Ndembi N, Habakkuk Y, Takehisa J. et al. HIV type 1 infection in Pygmy hunter gatherers is from contact with Bantu rather than from nonhuman primates. AIDS Res Hum Retroviruses 2003; 19:435-9.
6. Zhang YP and Ryder OA: Mitochondrial cytochrome b gene sequences of old World monkeys: With special references on evolution of Asian colobines. Primates 1998; 30:39-49.
7. Mahieux R, Chappey C, Georges-Courbot MC et al. Simian T-cell lymphotropic virus type 1 from Mandrillus sphinx as a simian counterpart of human T-cell lymphotropic virus type 1 subtype D.J Virol 1998; 72:10316-10322.
8. Salemi M, Van Dooren S, Audenaert E et al. Two new human T-lymphotropic virus type I phylogenetic subtypes in seroindeterminates, a Mbuti Pygmy and Gabonese, have closest relatives among African STLV-I strains. Virology 1998; 246:277-287.
9. Kimura M: A simple method for estimating evolutionary rates of substitutions through comparative studies of nucleotides sequences. J Mol Evol 1980; 16:111-120.
10. Saitou N and Nei M. The neighbor-joining method: A new method for reconstructing phylogenetic trees. Mol Bio Evol 1987; 4:406-425.
11. Peeters M, Courgnaud V, Abela B et al. Risk to human health from a plethora of simian immunodeficiency viruses in primate bushmeat. Emerg Infect Dis. 2002; 8:451-7.
12. Aghokeng FA, Liu W, Bibollet-Ruche F et al. Widely varying SIV prevalence rates in naturally infected primate species from Cameroon. Virology 2006. 345:174-189.

Table 1. Serological survey and nested PCR amplification of animal kept as pets in southern Cameroon

Species (common name)	SIV lineage	HIV-1/2 Ag/Ab Combo	Serology				Nested PCR amplification	
			AxSYM [a]	HIV-1 PA[b]	HIV-2 PA	HIV-1 WB[c]	pol-IN[d]	env-gp41
Mandrillus Sphinx (Mandrill)	SIVmnd-2	3/13 (Npos/Ntested)					3/13	0/13
		(1)-01cmr-202	44.9	256	512	(+/-gp160, gp110/120, p18)	SIVmndCM-202	(-)
		(2)-01cmr-211	16.7	< 32	512	(+/-p52, p34, p25, p18)	SIVmndCM-211	(-)
		(3)-01cmr-218	57.6	1024	2048	(+/-gp160, gp110/120, p18)	SIVmndCM-218	(-)
Cercopithecus nictitans	/	0/5	< 1.0	< 16	< 16	/	(-)	(-)
Pan troglodytes (Chimpanzee)	/	0/10	< 1.0	< 16	< 16	/	(-)	(-)

a) AxSYM HIV-1/2 , a microparticle assay EIA (Abbott, Tokyo, Japan); signal/cut-off >1.0 means reactive
b) Particle agglutination (PA), titer against HIV-1 or HIV-2. The antibody titer was measured according to manufacturer instructions. (Serodia HIV, Fujirebio, Tokyo, Japan)
c) New Lavblot HIV-1 and HIV-2 (Sanofi Pasteur, Marnes-la-Coquette, France)
d) Genotyping based on HIV pol-Integrase region (288bp)

title

Changes of erythrocytes corpuscular volume in HIV-infected patients on antiretroviral therapy

authors

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summary

Erythrocytes mean corpuscular volume (MCV) was assessed in HIV-infected patients receiving antiretroviral (ARV) treatment. The only noticeable cause of macrocytosis was the applied therapy, especially using thymidine analogues that inhibit viral reverse transcriptase. Erythrocytes volume depended on the degree of patient's adherence to therapeutic regime. RBCs volume normalization preceded detectable HIV viraemia. Authors suggest that therapy should be started with thymidine analogues (azidothymidine, stavudine), especially in potentially non-compliant patients. Such strategy could improve patients' adherence to therapy, enable introduce earlier motivational actions and help avoid unnecessary modifications of therapeutic regimens.

key words

HIV infection, antiretroviral therapy, red blood cells, corpuscular volume

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Background

Since introduction of active antiretroviral therapy, decreasing mortality and opportunistic infections rates in HIV-infected patients have been reported. At the same time, morbidity related to therapy and resulting from adverse events and treatment complications has become visible. Among other things, alterations concerning peripheral blood erythrocytes (RBCs) of patients receiving antiretroviral (ARV) therapy are being observed.

One of RBCs indices is mean corpuscular volume of the cell (MCV). Technologically advanced, modern haematological counters are able to perform measurements of a single red blood cell volume, and calculated MCV is a mean value of volumes of RBCs assessed. MCV serves mainly as a tool for definition of type of anaemia.

Increased RBCs volume (macrocytosis) can be found in about 1 to 3% of general population (1). The most common cause of macrocytosis, accounting for more than 35% of cases, is bone marrow dysplasia resulting from alcohol abuse. Other possible causes include vitamin B12 deficiency (present in 10 to 20% of HIV-infected patients), hypothyroidism, reticulocytosis following bleeding, aplastic anaemia, monoclonal gammapathy, liver diseases, myeloproliferative disorders (1, 2, 3). Increased MCV accompanies also some of therapies, especially anti-cancer ones (4). Increased MCV has been also reported in HIV patients treated with antiretroviral therapy (HAART), being attributed to azidothymidine (AZT) and, to a lesser extent, to stavudine (d4T) effects (5, 6, 7).

This paper focus on relations between MCV and different qualitative and quantitative characteristic features of treated population. Presence of illness-related factors, possibly influencing MCV as well as utility of MCV as a measure of patient's adherence to therapeutic regime (especially scheduled drug dosage) were also assessed.

Material and Methods

Seventy four patients (20 women, 54 men) aged from 23 to 65 (mean 35,6 ± 9,6 years) receiving antiretrovoral therapy for HIV infection in Acquired Immune Deficiency Outpatient Clinic in Poznan were studied. MCV was determined the day of beginning of HAART ('baseline'), and subsequently after 3, 6,and 12 months of treatment (mean value from these last three analyses was used for final assessment). MCV between 80 and 100 fl was considered normal; below 80fl the cell was classified as microcytic and above 100 fl – as macrocytic. MCV can be calculated from hematocrit value and RBCs count: MCV = [Ht (%) × 10] / [RBC (10-12)]. Haemoglobin concentration, CD4 lymphocytes count, as well as iron, vitamin B12 and thyroid hormones concentrations were also measured at baseline and during ARV therapy. Other variables taken into account included: age, gender, HIV infection advancement according to CDC criteria, time from beginning of ARV treatment, Retrovir (AZT) / Combivir (CBV) presence in therapeutic scheme and patients' adherence to therapeutic regime (including alcohol consumption). Information concerning these two latter parameters was gathered from patients or close relatives.

Statistical methods

To assess relationships between mean MCV and qualitative parameters, non-parametric tests were used: Mann-Whitney test, and, for comparison of mean MCV and MCV „0", Wilcoxon's test.

Relation between mean MCV and quantitative parameters was described by Spearman's rank correlation coefficient (mean MCV does not have normal distribution). Spearman's coefficient value ranges from -1 to +1. Values near zero signify no correlation and closer to the limits – increasing relation between the assessed variables. Negative values denote inverse correlation.

Patients' compliance was assessed on the basis of interviews during control visits – number of missed or delayed doses of AVR drugs were taken into account.

Results

Relations between MCV and qualitative parameters are presented in table 1.

Gender did not influence MCV ($p = 0{,}318$). Increase in red blood cell volume did not depend on the disease's stage (difference between clinical stage A and C; $p = 0{,}434$). There was found that AVR introduction caused statistically significant increase in MCV ($p < 0{,}001$). The difference between patients, in whom AZT or CBV was used in the treatment scheme, and people whose therapy did not contain these drugs was demonstrated ($p = 0{,}024$). Statistically significant changes of RBC volume during HAART therapy in patients not receiving AZT/CBV was found ($p < 0{,}001$). No influence of alcohol consumption nor degree of patient's adherence to treatment was stated ($p = 0{,}129$ and $p = 0{,}377$, respectively).

Table 2 presents relationship of RBC volume and qualitative parameters of studied patients.

Mean RBCs volume increased significantly during HAART therapy, as compared with baseline values ($p = 0{,}001$). CD4 lymphocytes count, both at baseline, and during therapy, did not influence MCV ($p = 0{,}104$ and $p = 0{,}094$, respectively). Anaemia was diagnosed in one patient during ARV therapy; in this case erythrocytes volume was at the upper limit of normal. No correlation between haemoglobin concentration at baseline and during treatment, was demonstrated ($p = 0{,}969$ and $p = 0{,}552$, respectively). RBCs volume did not depend on the duration of treatment with HAART ($p = 0{,}583$), mean ARV treatment time being 3 years (from 3 to 100 months). Correlation between iron and vitamin B12 serum concentrations and MCV turned out also to be of no statistical significance ($p = 0{,}637$ and $p = 0{,}986$, respectively). TSH and thyroxin concentrations were mildly elevated in two cases, without clinical signs nor symptoms. No correlation between TSH or FT4 and MCV was found ($p = 0{,}872$ and $p = 0{,}872$, respectively).

Table 1. Relationship between MCV and patients' gender, stage of HIV infection, adherence to therapy, HAART treatment, presence of AZT or CBV in therapeutic regimen (Mann-Whitney test; Wilcoxon's test for comparison of MCV with MCV „0")

Parameter		N	Mean ± SD (fL)	Median	Minimum	Maximum	p
Gender	F	20	108,5 ± 9,6	111,7	86,0	120,7	0,318
	M	54	106,7 ± 9,6	106,8	66,1	128,7	
CDC stage	A	56	107,6 ± 9,5	107,8	66,1	126,7	0,434
	B	3	105,5 ± 1,8	104,7	104,3	107,5	
	C	15	105,9 ± 11,0	106,0	86,0	128,7	
Adherence	good	64	107,6 ± 9,5	107,3	66,1	128,7	0,377
	bad	10	104,4 ± 10,3	106,0	89,2	119,1	
Alcohol	no	58	108 ±8,6	107,8	86,0	128,7	0,129
	suspicion	11	101,3 ±13,5	106,0	66,1	116,0	
	abuse	5	110 ±7,5	111,0	98,7	119,1	
HAART	MCV„0"	64	88,2 ± 11,6	90,2	80,9	106,2	< 0,001
	MCV	64	107,3 ± 9,7	107,3	66,1	128,7	
AZT/CBV present	no	44	105,3 ± 10,2	105,3	66,1	128,7	0,024
	yes	30	109,9 ± 8,0	110,0	86,0	126,7	
HAART w/out AZT/CBV	MCV„0"	35	88,8 ± 15,3	92,0	80,9	106,2	< 0,001
	MCV	35	105,2 ± 10,4	105,0	66,1	128,7	

Table 2. Relationship between MCV and qualitative parameters

Parameter	N		Mean ±SD (fL)	Median	Minimum	Maximum	Parameter vs. MCV	
							rs*	p**
age	F	20	32,7 ±5,4	33	23	44		
	M	54	38,0 ±8,5	38	24	65	0,053	0,651
CD4„0" k/mm3	F	20	190,8 ±89,6	211,5	21	321		
	M	54	146,1 ±134,3	100,0	2	593	0,192	0,104
CD4 k/mm3	F	20	413,8 ±219,5	401,5	74	917		
	M	54	410,8 ±203,8	408,0	37	847	0,198	0,094
HAART (months)	F	20	34,3 ±24,5	30,0	5	99		
	M	54	38,8 ±26,9	35,5	3	100	0.065	0,583
Hb„0" (mmol/l)	F	18	7,7 ±0,9	7,7	6,2	9,0		
	M	46	7,9 ±1,3	8,4	4,8	9,8	0,005	0,969
Hb (mmol/l)	F	20	8,4 ± 0,7	8,3	7,5	10,0		
	M	54	9,8 ±4,4	9,2	6,0	10,2	-0,074	0,552
Fe (µg%)	F	19	109 ±48,5	88	40	239		
	M	52	121,1 ±49,5	108,5	59	271	0,057	0,637
Vit B12 (pg/ml)	F	20	374 ±124,1	329	219	677		
	M	54	365,7 ±163,7	330,5	132	1200	0,002	0,986
TSH (mU/l)	F	13	1,5 ±0,8	1,5	0,6	3,3		
	M	33	1,9 ±1,4	1,8	0,3	7,6	-0,024	0,872
FT4 (pmo/l)	F	13	15,2 ±4,2	14,9	7,9	22,1		
	M	33	14,4 ±3,8	14,4	8,0	21,0	0,093	0,539
MCV "0" (fl)	F	18	88,9 ±5,4	90,2	79,8	98	x	x
	M	46	88,0 ±13,3	90,1	79,1	106,2		
MCV (fl)	F	20	108,5 ±9,6	111,7	86,0	120,7		
	M	54	106,7 ±9,6	106,8	66,1	128,7	0,392	0,001

* – Spearman rank correlation coefficient

** – level of significance

Reference values ranges:

Hb (mmol/l): F: 6,8-9,31 M: 7,45-10,55
MCV (fL) 80-92
Fe (µg%) F: 37-145 M: 59-158
Vit B12 (pg/mll) 280 – 568
TSH (µU/ml): 0,3 – 4,0
FT4 (pmo/l): 7,8 – 19,4

Discussion

Most often, increase in erythrocytes volume is accompanied by anaemia, in our group, however, except one patient with advanced, drug-resistant AIDS, no anaemia was detected. Patients were examined for other possible causes of macrocytosis. Vitamin B12 deficiency was demonstrated in 4 patients, in others, vitamin B12 concentration was normal or above normal. Some of them, without treating physician's consent, self-medicated themselves with this vitamin preparations. In all patients thyroid function was normal. No statistical significance of differences between MCV in patients with known alcohol abuse problem and other patients resulted from impossibility of objective assessment of alcohol consumption, but also indicated presence of other cause of macrocytosis. Such cause, present in majority of our patients, was ARV therapy, role of which was described in the literature, especially in connection with zidovudine and stavudine therapy (5, 6, 7).

Mechanism of MCV increase is not elucidated (8). Folate deficiency is frequently reported in heavy drinkers, as alcohol increases folate requirements and impairs its metabolism. Macrocytosis may be present in people with folate deficiency, as well as in those receiving folate supplementation. In patients abusing alcohol, its toxic action on marrow progenitor cells (by alterations of fatty acids/lipids composition and hydration of RBCs membrane) may lead to macrocytosis. The mechanism of action of ARV drugs on red blood cells is also not fully understood (9). Some authors suggest the role of mitochondrial toxicity (10, 11), others attribute erythrocytes volume increase to zidovudine monophoshates concentration (8, 12). In spite of clearly restraining influence of nucleoside reverse transcriptase inhibitors on mitochondrial DNA polymerase synthesis, mitochondrial dysfunction was alsoreported in HIV-infected patients not receiving HAART therapy (13, 14, 15). This suggests the possibility that HIV infection itself may play a role in these events.

As a mechanism of macrocytosis development is unclear, its clinical significance remains unclear(9). In our study, no correlation between MCV and adverse events rate was demonstrated. There was noticed, however, that macrocytosis correlates with patients' compliance and adherence to therapeutic regime (7,16). Division of patients into 'adherent' and 'non-adherent' was based on patients' self-reports. There was reported in the literature, that results of self-evaluation of patients correlated well with HAART therapy effectiveness (16), which was not in our study.

Such subjective methods of adherence assessment are unfortunately seldom reliable. Patients frequently did not admit missed drug doses and reported false data. Not infrequently, return of increased MCV values to normal during HAART therapy preceded detectable HIV viraemia in subsequent analysis, often with decrease in CD4 lymphocytes count. At the same the patient claimed, that she/he has been taking medicines as prescribed. Only in the face of treatment failure these patients admitted, that they frequently delayed or missed their drugs doses. These observation confirms that MCV assessment may be helpful in determining patient's adherence to treatment (17,18). This simple method may be of great help, especially that HAART monitoring tests (CD4/CD8 lymphocytes count and HIV-RNA) is performed in Poland on average twice a year, and therapy failure is usually diagnosed rather late. Rapid normalization of erythrocytes volume, when resulting from patient's lack of discipline, allows motivational actions to be undertaken. This can maintain efficacy of therapeutic scheme used, and leave other drugs for the future.

There was also observed that some antiretroviral drugs, such as Viread and Emtriva influence erythrocyte volume to the lesser extent. These drugs are currently recommended for initial therapy (19). It seems however. that inclusion of zidovudine / stavudine during fist months of HAART therapy is helpful in assessment of patient's adherence to treatment. If no MCV increase is noted, greater stress should be put on patient's education, including the reasons of high requirements towards a person treated with ARV and description of consequences in case of neglecting the treatment. Early education to increase patient's motivation to therapy may allow to avoid premature modifications of treatment schemes, which failure is attributed to every other cause than the patient himself. It does matter, having in mind also the costs of genetic typing of HIV.

Conclusions

1. The only noticeable cause of macrocytosis in the studied group were thymidine analogues used in antiretroviral therapy.
2. Patients self-evaluation concerning adherence to treatment were not reliable in HAART therapy practice.
3. Introduction of thymidine analogues to initial therapy may be helpful in objective assessment of patient's compliance, enable introduce earlier motivational actions and help avoid unnecessary modifications of therapeutic regimens, as well as expensive diagnostic procedures in search of causes of therapy failure.

References

1. Hoffbrandd V, Provan D: ABC of clinical haematology. Mcrocytic anaemias; Brit Med J 1997
2. Horstman AL, Serck SL, Go RS: Macrocytosis associated with monoclonal gammopathy;Eur J Haemat 2005, 75, 146-9.
3. Remacha AF, Cadafalch J: Cobalamin deficiency in patients infected with the human immunodeficiency virus., Semin Hematol 1999; 36: 75-87
4. Karvellas C, Sawyer M, Hamilton M, Mackey JR: Effect of Capecitabine on Mean Corpuscular Volume in Patients With Metastatic Breast Cancer; Am.J.Clin.Oncol., 27 (4):364-8
5. Volberding PA, Lagacos SW,Koch MA et al. Zidovudine in asymptomatic human immunodeficiency virus infection. The Aids Clinical Trial Group, N.Eng J Med 1990
6. Simon D, Johns D: Mitochondrial disorders: clinical and genetic features. Ann Rev Med 1999, 50, 111-27
7. Romanelli F, Empey K, Pomeroy C: Macrocytosis as an indicator of medication (zidovudine) adherence in patients with HIV infection; AIDS Pat.Care STDS, 2002 Sep; 16 (9): 405-11
8. Tornevik Y, Ullman B, Balzarini J et al. Cytoticity of 3'-azido-3'deoxythymidine correlates with 3'-azidothymidine-5'-monophosphate (AZTMP) levels, whereas anti-human immunodeficiency virus (HIV) activity correlates with 3'-azidothymidine-5'-triphosphate (AZTTP) levels in cultured CEM T-lymphoblastoid cells, Biochem Pharmacol 1995;49,829-37
9. Genne D, Sudre P, Anwar D,et al. Causes of macrocytosis in HIV-infected patients not treated with zidovudine, J Infect, 2000;40,160-3
10. Brinkman K, Hofstede J, Burger D et al: Adverse effects of rev erse trancriptase inhibitors: mitochondrial toxicity as comon pathway; AIDS, 1998, 12, 1735-44
11. Brinkman K, Smeitink J Romijn J, Reiss P: Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy; Lancet 1999, 354, 1112-5.
12. Stein DE, Moore KH: Phosphorylation of nucleoside analog

antiretrovirals: a review for clinicians; Pharmacotheraphy 2001,21, 11-34
13. Cherry CL, Wesslingh SL: Nucleoside analogues and HIV: the combined cost to mitochondria, J Antimicr Chemoth, 2003, 51, 1091-3
14. Chattha G, Arieff AI, Cary C, Tierney LM: Lactic acidosis complicating the acquired immunodeficiency syndrome, Ann Int Med, 1993, 118, 37-9
15. Shikuma CM, Hu N, Milne C et al.: Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatophy, AIDS, 2001, 15, 1801-9
16. Duong M, Piroth L, Peytavin G et al: Value of Patient Self-Report and Plasma Human Immunodeficiency Virus Protease Inhibitor Level as Markers of Adherence to Antiretroviral Therapy: Relationship to Virologic Response;Clin Inf Dis, 33 (2001,386
17. Petersen K, Hale R, Wallace MR. Macrocytosis after nucleoside-containing HIV treatment regimens, Infect Dis Clin Pract, 2005; 13, 65-7
18. Romanelli F, Empey K, Pomeroy C, Macrocytosis as an indicator of medication (Zidovudine) adherence in patients with HIV infection, AIDS Pat Care and STD, 2002;16,9, 405-11
19. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, DHHS Panel, editorial, october 2006, http://AIDSinfo.nih.gov

title

The Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV infected patient – case report

authors

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summary

The Immune Reconstitution Inflammatory Syndrome (IRIS) runs atypically in HIV/AIDS patients at early stage of antiretroviral therapy (ART). Beside confirming reports of the effectiveness of this therapy i.e. – lower viral load (VL) and increase of the number of CD4 lymphocytes we have to remember about IRIS. Often the clinical symptoms are non-specific, as in some opportunistic infections or different chronic diseases with inflammatory reaction.

key words

HIV infection, Acquired Immune Deficiency Syndrome (AIDS), Immune Reconstitution Inflammatory Syndrome (IRIS), Antiretroviral Therapy (ART), cytokines, opportunistic infections

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Abstract

Despite many reports about the benefits of antiretroviral therapy (ART) i.e.- reduction of viral load and higher counts of CD4 we should remember about immune restoration (IRIS) phenomenon. IRIS occurs as an atypical inflammation in HIV/AIDS patients at early phase of treatment. Clinically IRIS can presents unusual symptoms as in some opportunistic infections or other chronic infectious diseases with inflammatory response.

Case report

A 18 year-old-man N.P.N. an intravenous drug user was admitted in June 2004 to the Departament of Hepatology and AIDS, Institute for Infectious and Parasitic Diseases, Warsaw Medical University because of symptoms: fever periodically crossing 40,0°C, dry tiring cough, abdominal pain, nausea, vomiting and diarrhea.

The physical examination revealed cachexia – weight 40,0 kg at height 176,0 cm, muscular atrophies, enlargement of peripheral lymph nodes and crepitation over lungs. Performed ELISA HIV – antybody test was positive and was confirmed by Western Blot. In the initial immunological (Table 1) investigation – CD4 count was 125 cells/µl, CD8 – 433 cells/µl, CD4/CD8 ratio – 0,29 and the HIV Viral Load (VL) – was more than 100000,0 copies/ml. CMV IgM, Toxo IgG, IgM antibodies were negative but CMV IgG was positive. The blood cultures for bacteria and fungi reminded sterile but Mycobacterium tuberculosis (miliary tuberculosis) pulmonary infection as well as chronic HCV hepatitis were diagnosed.

Initially prescribed tuberculostatic treatment included: Isoniazid, Ethambutol, Streptomycine and Ofloxacine. The patient was resistant to Rifampicin and Pyrazinamid.

In November 2004 total CD4 lymphocyte count was 89 cells/µl, CD8-957 cells/µl, CD4/CD8-0,09 and the HIV VL (*Viral Load*) more than 100000,0 copies/ml. The ART therapy was initiated with two NRTIs (*NRTI – Nucleoside reverse transcriptase inhibitors*) i.e.: Combivir (contains Zidovudine and Lamivudine, 3TC) (both NRTI) – 1 tablet twice daily and Kaletra (contains Lopinavir and Ritonavir) both *(PI – Protease inhibitors)* – 3 capsules twice daily. In December 2004 after about 4 weeks of ART therapy worsening of general state of the patient was recorded. The main symptoms were: temperature to 40,0°C, meningeal symptoms, epilepsy, strong headache, deterioration of vision of right eye, loss of the body weight about 10,0 kg.

In serological tests for antibodies: CMV IgM, anti-Toxoplasma IgG and IgM, anti-HBc total were negative. Only one serological result for anti-CMV IgG antibodies was positive. The CSF (*cerebro-spinal fluid*) culture with MTD (*Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test*) method confirmed Mycobacterium tuberculosis infection. At the same time the following complications were diagnosed:

- Toxoplasma gondii brain abscess (see scan 1 and 2)
- CMV retinitis

The ART therapy was withdrawn. Beside tuberculostatic drugs also the other medications were prescribed i.e., Cytovene (Gancyclovir), Sulphadiazine, Antrex (Calcium folinate), Pyrimethamine (Daraprim), Dexamethasone (Decadron), Fluconazole. Within next few weeks improvement of the clinical state of the patient was recorded. CT scan of CNS – revealed total regress of abscess as well as inflammation.

After about 2 weeks the clinical condition of the patient improved. The next ART therapy was initiated about 8 weeks later but in a different combination with: Zerit (*Stavudine*) twice daily and Epivir (Lamivudine, 3TC) twice daily (both NRTI), Stocrin (*Efavirenz*) once daily 600 mg. (*NNRTI – Non-nucleoside reverse transcriptase inhibitors*). After about 2 weeks of therapy general condition of the patient became worse again but the ART treatment was continued. In May 2005 patient was discharged from the hospital and till date remains in outpatient clinic care. One month later the total CD4 count increased to 196 cells/ml, CD8 count was – 547 cells/ml and HIV viral load below detection level (< 50 copies/ml).

***

Already in 1997 it was clear about new symptoms in HIV/AIDS patients on antiretroviral therapy appearing in the first months of ART therapy. It was observed that inclusion of antiretroviral therapy can carry itself risk of activating opportunistic infections, deterioration of liver functions in HBV, HCV co-infected patients. Facts turned attention, that above mentioned symptoms appeared not only in patients with rising CD4 count but also when level CD4 did not undergo changes during the course of therapy. IRIS appeared often from about 4 weeks to even 12 months from the beginning of the therapy. But was reported already after 10 days from the onset of therapy **(1).**

An atypical course of HCV and HBV coinfection in HIV infected patiens was described in a period of 6 months from inclusion of ART therapy **(2, 3)**.

In one work, case report was submitted where the patient with HIV and TB after 12 months of effective ART and anti – TB therapy demonstrated IRIS. Suggesting symptom of IRIS was rupture of the large intestine with severe inflammatory reaction **(4).**

Frequency of occurrence of this syndrome estimates about 10-25 % among treated patients but there is no large clinical investigation about the scale of this problem **(2).** To describe this syndrome different synonyms were used: IRIS (*Immune Reconstruction Inflammatory Syndrome*), IRD (*Immune Restoration Disease*) or IRS (*Immune Reconstitution Syndrome / Immune Recovery Syndrome*) **(3).** Syndromes reminding IRIS at patients were described earlier in HIV sero-negative patients (Table 2). For example: in patients on antibiotics during the course of treatment of multibacillary lepromatous lepra as "reversal reaction of leprosy", as well as during steroid therapy.

Regimens of ART Therapy

Different regimens of antiretroviral therapy are applied both in initiating treatment as well as continuing of treatment. Decision about regimen of ART drugs doctors take after exact analysis of CD4, VL, clinical state, current complications etc. Particularly the most important is the first therapeutic regimen, because it has the best chance to effectively slow down the disease progression.

<u>Groups of antiretroviral drugs available at present:</u>

- Nucleoside reverse transcriptase inhibitors – NRTI
- Non-nucleoside reverse transcriptase inhibitors – NNRTI
- Nucleotide reverse transcriptase inhibitors NtRI
- Protease inhibitors (PI)
- Hydroxyurea agents
- Fusion inhibitors
- Chemokin receptor antagonists

- Inhibitors of transcription
- Integrase inhibitors
- Immunomodulators, vaccines

The ART therapy contains at least 3 drugs and it is possible to widen the combination. Composition of ART drugs has significant meaning in avoiding IRIS. Till date not all risk factors for IRIS has been disclosed. But it has been observed that therapy on the basis of two Protease Inhibitors – PI in comparison with different other groups i.e. NRTI, NNRTI has a better course, inhibits VL and causes total reconstruction of immune system with a little risk of IRIS. Such situation observed both in patients with acute HIV infection as well as in patients living with HIV for years **(5).**

Therefore to avoid the onset of IRIS the ART therapy should include 2 protease inhibitors. Antiretroviral therapy in patients with HIV is significantly effective in lowering viral load (VL) of HIV RNA and stimulating rise of CD4 count. Considerable decreased morbidity and mortality in patients from AIDS **(6,7).** Different therapeutic antiretroviral regimens effectively inhibits the progress of disease. Though during the course of ART therapy we observe rise in number of CD4, decreased level of VL but not all functions of immune system come back to norm. Some mechanisms of immunological functions disappear irreversively, new functions approach to create immunological balance in organism of infected person with HIV. The influence of individual ART drug in human immune system is not well-known. The exact time for initiating of ART is still a controversial issue among physicians involved in HIV/AIDS management. Followers of "early" introduce of ART have so much strong arguments as their opponents. But risk of IRIS argues to early initiation of ART therapy (Table 4).

Though in one publication **(8)** the authors during 4-years of effective antiretroviral therapy observed no ability to immune reconstruction depended only on CD4 cell-count, but too late inclusion of ART treatment e.g. when CD4 < 50 cells/ml can bring into situation, in which some functions of immune system become permanently damaged despite of the return of CD4 count to proper value **(9).** Antiretroviral therapy introduced in early stage of infection causes complete return of immune function despite delay in reconstruction of the number of circulating CD4. No differences of the CD4 level in intestine (biopsy) and in blood were noted in persons with slow progression of HIV infection **(10).**

Opportunistic Infections

Some of diseases have connection with onset of IRIS in HIV positive patients (Table 3). Domingo et al. observed 24 cases of Herpes zoster infection among 316 patients after four months from the beginning of ART. Moreover it was shown, that in these patients peripheral blood CD8 count was significantly higher than in patients without such infection **(11)**. Within a period of 6 months after inclusion of effective ART therapy atypical courses of different infections were described i.e.: Cytomegaloviral (CMV) **(12, 13, 14)**, Mycobacterium tuberculosis (TB) **(15)**, Mycobacterium avium complex (MAC) **(16, 17)** and mycosis – Cryptococcus neoformans **(18, 19).**

As a manifestation of IRIS, infection of parvovirus B19 in a patient in four weeks after inclusion of ART therapy was detected. Nolan et al described a young male who developed RBC (red blood cells) aplasia and a painless, progressive dyspraxia of the left arm and expressive dysphasia 4 weeks after commencing effective ART therapy. CNS imaging demonstrated multiple right fronto-parietal lesions, and brain biopsy concluded the association of lesions with parvovirus B19 infection **(20).** Intensifications of neurological symptoms in a patient with progressive multifocal leucoencephalopathy (PML) and worsening of clinical condition was also described **(21).**

The role of cytokines

It was confirmed, that in HIV infected patients with IRIS plasma level of antagonists of receptor IL-1, TNF, CD8 and CD38 is considerably higher than in patients without IRIS (control group). This can push conclusion, that cellular markers of immunological reaction are disturbed only in some of the patients with good response to ART therapy and may have relationship with episode of IRIS **(22). A**fter initiation of ART therapy the rise in CD4 goes on in following stages **(23):**

- **Stage 1.** Freeing of T lymphocytes from spare pool
- **Stage 2.** Formation of naive T lymphocytes in regions not yet disclosed.

In early stages of immune reconstruction CD4 cells are freed from spare pool. This mechanism is common in all morphological elements of blood and observed not only in patients on ART therapy. Enigmatical function is carried by thymus gland in the second stage of immune reconstruction process. Control of synthesis and maturation of lymphocytes T (including CD4) take place in thymus gland, organ, which in childhood beside marrow takes main part in lymphopoiesis, disappears in adult age. Mc Cune et of al. **(24)** observed increase weight of thymus gland in accordance with the rising number of naive CD4 cells in patients after initiation of ART therapy.

According to publication of Carcelain G et al after introduction of ART therapy the viral load is suppressed, which reduces the viral burden on thymus gland causing stimulation of thymus gland. This can stimulate production CD4, which come under redistribution to circulation **(25).** Above mentioned mechanisms are observed exclusively during the course of long-term activation of T lymphocytes **(23).**

In some of the patients after inclusion of antiretroviral treatment number of CD4 slightly rises with effective virological response i.e. VL < 50 copies of HIV RNA/ml. Thymus dysfunction may be the cause of this phenomenon **(26).**

Special attention was given to IL-2 in view of it's active part in process of synthesis of CD4 lymphocytes. In one work the authors analyzed the impact of IL-2 on the synthesis of CD4 lymphocytes in patients on ART therapy. The groups of analyzed patients were naïve to the ART therapy. In the first group patients received only ART drugs (Lamivudine (3TC) or Lamivudine 3TC and Zerit (Stavudine, d4T) or Zerit (Stavudine, d4T) and Crixivan (Indinavir). In the second group together with ART drugs, IL-2 were included for a period of 4 weeks. In patients receiving IL-2, value of CD4 lymphocyte increase was significantly higher. However in both groups viral suppression was comparable. Applying of ART drugs in combination with IL-2 is promising, but it is not sure whether this will be recommended in treatment of all HIV infected patients. **(27).**

In an investigation led by Martin et al. in a period of 1-year the change in T lymphocyte pool was observed: patients included to this investigation demonstrated undetectable VL after 4-months therapy, low activation of naive T (CD4) lymphocyte pool, little activation of CD8 and weaken repopulation of CD4 lymphocytes producing IL-2 and IFN-gamma. Moreover patients, who were already on ART therapy earlier showed little immunological changes than naïve patients. In patients with light immunological

reconstruction VL was undetectable for 12 months. Investigations showed, that long time suppression of HIV VL can make possible effective reconstruction of immune function and return to normal activity **(28).** Patients with HIV and IRIS (e.g. HSV infection) have higher level of IL-6 and soluble IL-6 in serum than in patients who did not demonstrate IRIS in past **(29, 30).**

The knowledge about changes in immune system of HIV/AIDS patients, bone marrow was also analysed comparing intensification of apoptosis and lymphopoesis of T cellular line. The results of investigations confirmed, that intensification of apoptosis has relationship with intensification of lymphopoesis. Strong relationship (inversely proportional) was observed between in vitro apoptosis of lymphocytes T and number of peripheral T lymphocytes. Stimulating mechanisms of apoptosis observed in HIV positive patients were better described **(31).** The ART therapy may interfere in the activity of marrow stem cells because during the course of therapy synthesis of hematopoetic inhibitors is decreased **(32).**

Treatment of IRIS

Suggested treatment for IRIS includes: immunosuppressive drugs (steroids), anti-inflammatory drugs and supportive therapy **(33).** In a work by Shelburne S. et al many patients were described because of IRIS. Very often recurrent atypical course with acute inflammation was observed – caused by among others: Mycobacterium tuberculosis, Cryptococcus neoformans or CMV.

In treatment of such complications authors applied: first of all continuing ART therapy, primary prophylaxis against given pathogens as well as of anti-inflammatory drugs. Ability to demonstrate strong inflammatory response permits in many patients considering of the legitimacy of continuing secondary prophylaxis particularly when the number of CD4 lymphocytes reaches approximately to proper values **(13)**.

Conclusion

The Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV infected patients usually takes place during effective ART therapy. It is not possible to foresee, in which patient this syndrome will take place. Potentially patients with lower CD4 count at the time of initiating ART therapy are at higher risk and the first months of therapy of ART should be very carefully monitored.

Nonspecific symptoms, atypical course makes it difficult to put proper diagnosis. Treatment of IRIS is practically complex why it should be remembered that IRIS may happen during the course of antiretroviral therapy and symptoms are quite different from those recognized as the side effects of the ART therapy.

References

1. Buckingham SJ, Haddow LJ, Shaw PJ, Miller RF. Immune reconstitution inflammatory syndrome in HIV-infected patients with mycobacterial infections starting highly active anti-retroviral therapy. Clin. Radiol. 2004 Jun;59(6):505-13.
2. Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol. 2001 Oct; 22(3): 279-287.
3. Rouanet I, Peyriere H, Mauboussin JM, terrail N, Vincent D. Acute clinical hepatitis by IRS in a HIV/HBV co-infected patient receiving antiretroviral therapy. Eur J Gastroenterol Hepatol. 2003 Jan 15(1):95-97.
4. Guex AC, Bucher HC, Demartines N, Fluckiger U, Battegay M. Imflammatory bowel perforation during immune restoration after one year of antiretroviral and antituberculous therapy in an HIV-1 infected patient: case report. Dis Colon Rectum.2002 Jul;45(7):977- 978.
5. Dyer W.B., Kuipers H., Coolen M.W., Geczy AF., Forrester J. Workmann, Sullivan JS. Correlates of antiviral immune restoration in acute and chronic HIV type 1 infection: sustained viral suppression and normalization of T cell subset. AIDS Res Hum Retroviruses. 2002 September 20;18(14):999-1010.
6. Palella FJ Jr, Delaney KM, Moorman AC I wsp. Declining morbidity and mortality among patients with advanced HIV infection. NEJM 1988; 338: 853-860.
7. Vittinghof E, Scheer S, O`Malley P I wsp. Combination therapy and recent declines in AIDS incidence and mortality. J Infect Dis 1999;179:717-720.
8. Hunt PW, Deeks SG, Rodriguez B, Valdez H¸ Shade SB, Abrams DI, Kitahata MM et al. Continued CD4 cell count increases in HIV infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS 2003 Sep 5;17(13):1907-1915.
9. Lange CG, Lederman MM, Medvik K, Asaad R, Wild M, Kalayjian R, Valdez H. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cell predict functional responses to immunizations in chronic HIV infection, AIDS 2003 Sep 26;17(14):2015-2023.
10. Guadalupe M, Reay E, Sankaran S, Prindiville T, Flamm J, McNeil A, Dandekar S. Severe CD4+ depletion in gut lymphoid tissue during primary HIV 1 infection and substantial delay in restoration following HAART. J Virol. 2003 Nov; 77(21): 11708-11717.
11. Domingo P., Torres OH., Ris J., et al. Herpes zoster is an immune reconstitution disease after initiation of combination anti-retroviral therapy in patients with human immunodeficiency virus type-1 infection. Am J Med. 2001; 110: 662-663.
12. Qazi NA, Morlese JF, Walsh JC, Bunkier CB, Francis N, Nelson MR. Case report.Severe cutaneous ulceration secondary to cytomegalovirus inclusion disease during successful immune reconstitution with HAART. AIDS Read. 2002 Oct; 12(10):452-4, 456-457.
13. Shelburne SA 3rd, Hamill RJ. The immune reconstitution syndrome, AIDS Rev. 2003 Apr – Jun 5(2):67-79.
14. Stone SF, Price P, Tay-Kearney ML, French MA. Cytomegalovirus (CMV) retinitis immune restoration disease occurs during highly active antiretroviral therapy-induced restoration of CMV-specific immune responses within a predominant Th2 cytokine environment. J Infect Dis. 2002 Jun 15; 185(12): 1813-1817. Epub 2002 May.
15. Schluger NW, Perez D, Liu YM. Reconstitution of immune response to tuberculosis in patients with HIV infection who receive antiretroviral therapy. Chest. 2002 Aug;122(2):597-602.
16. De Paoli P., Bortolin M.T. Zanussi S., Monzoni A, Pratesi C, Giacca M. Changes in thymic function in HIV-positive patients treated with highly active antiretroviral therapy and IL-2. Clinical & Experimental Immunology 2001 September.125; 3: 440.
17. Hassell M, French MA. Mycobacterium avium infection and immune restoration disease after highly active antiretroviral therapy in a patient with HIV and normal CD4+counts. Eur J Clin Microbiol Infect Dis. 2001 Dec; 20(12): 889-891.
18. Gąsiorowski J., Szybejko-Machaj G., Machaj A., Skórna postać kryptokozy u pacjenta z AIDS. Pol. Merk. Lek. 2001. X. 60. 456-459.
19. Jenny-Avital ER, Abadi M, Immune reconstitution cryptococcosis after initiation of successful HAART. Clin Infect Dis. 2002 Dec 15;35(12):128-133. Epub 2002 Nov 20.
20. Nolan RC, Chidlow G, French MA. Parvovirus B19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for human immunodeficiency virus infection. Clin Infect Dis. 2003 May 1; 36(9): 1191-1194. Epub 2003 Apr.

21. Safdar A., Rubocki RJ., Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunedeficiency virus type-1 infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy – associated immune reconstitution. Clin Infect Dis. 2002 Nov 15;35(10):1250-1257. Epub 2002 Oct 28.
22. Almeida CA, Price P, French MA, Immune activation in patients infected with HIV-1 and maintaining suppression of viral replication by HAART. AIDS Res Hum Retroviruses 2002 Dec 10;18(18):1351-1355.
23. Tubiana R., Carcelain G., Mohand H.A, Li TS, Renaud M, Blanc C, Calvez V et al., Immunologic reconstruction after antiretroviral treatment, Presse Med. 1999 February 27;28 (8):424-428.
24. Mc Cune JM, Loftus R., Schmidt Carell P, Webster D et al. High prevelance of thymic tissue in adults with HIV-1 infection. J Clin Invest 1998, 101:2301-2308.
25. Carcelain G., Debre P., Autran B. Reconstitution of CD4+ lymphocytes in HIV-infected individuals following antiretroviral therapy. Current Opinion in Immunology 2001, 13:483-488.
26. Teixeira L. Valdez H, Mc Cune JM, Koup RA, Badley AD, Hellerstein MK i wsp. Poor CD4 T cell restoration after suppression of HIV-1, AIDS, 2001 Sep 28;15(14):1749-56.
27. Levy Y., Kurier C., Krzysiek R., Rabian C, Capitant C Lascaux AS, Michon C et al. Effects of IL-2 therapy combined with highly active antiretroviral therapy on immune restorarion in HIV-1 infection: a randomized controlled trial. AIDS. 2003 February 14;17(3):343-351.
28. Martin M., Echevarria S., Leya-Cobian F., Pereda I., Lopez-Hoyos M. Limited immune reconstitution at intermediate stages of HIV infection during one year of highly active antiretroviral therapy in antiretroviral naïve versus nonnaïve adults. Eur J Microbiol Infect Dis. 2001 December; 20(12):871-879.
29. Stone SF, Price P, Keane NM, Murray RJ, French MA. Levels IL-6 and soluble IL-6 receptor are increased in HIV patients with history of immune restoration disease after HAART, HIV Med. 2002 Jan; 3(1):21-27.
30. Stone SF, Price P, Brochier J, French MA. Plasma bioavailable IL-6 is elevated in HIV patients who experience herpesvirus – associated immune restoration disease after start of HAART. J Infect Dis. 2001 Oct 15;184(8):1037-1037.Epub 2001 Sep 13.
31. Donnenberg AD, Margolick JB., Beltz LA., Donnenberg VS., Rinaldo Jr. Apoptosis parallels lymphopoiesis in bone marrow transplantation and HIV disease. Res Immunol. 1995 January;146(1):11-21.
32. Isgro A, Mezzoroma I, Aiuti A, De Vita L., Franchi F i wsp. Recovery of hematopoietic activity in bone marrow from HIV-1 infected patients during HAART. AIDS Res Hum Retroviruses 2000 Oct 10;16(15):1471-1479.
33. French MA. Antiretroviral therapy. Immune restoration disease in HIV-infected patients on HAART. AIDS Read. 1999 Nov;9(8):548-549, 554-555, 559-562.
34. Stoll M., Schmidt RE., Immune Restoration Inflammatory Syndromes: The Dark Side of Successful Antiretroviral Treatment Current Infectious Disease Reports, Volume 5, Number 3 / May 2003, 266-276.

Table 1. Biochemistry and immunology follow up

	24.06.2004	19.11.2004	23.06.2005	26.10.2005	02.02.2006
CD4 (cells/µl)	125,0	89,0	196,0	217,0	233,0
CD8 (cells/µl)	433,0	957,0	547,0	821,0	697,0
CD4/CD8 ratio	0,3	0,1	0,4	0,3	0,3
VL (copies/ml)	> 100000,0	> 100000,0	< 50,0	< 50,0	< 40,0
ALT (IU/ml)	19,0	13,0	56,0	36,0	84,0
AST (IU/ml)	35,0	18,0	51,0	49,0	72,0
ALP (IU/ml)	110,0	73,0	101,0	87,0	135,0
GGTP (IU/ml)	118,0	20,0	703,0	710,0	539,0

Table 2. Situations, which can initiate onset of IRIS (4)

Control of disseminated infection by potent antimicrobial chemotherapy
"Reversal reaction" after treatment of lepromatous lepra
Development of cerebral tuberculoma under tuberculostatic treatment
Interruption of long-term immunosuppressive treatment, eg, with corticosteroids
Initiation of ART therapy in HIV infection, highest risk in patients with:
- Advanced immunodeficiency
- Pre-existing opportunistic infection

Certain patterns or subgroups of immune restoration
Genetically restricted risk factors (eg, human leukocyte antigen haplotypes, interferon – genotypes)
Reconstitution of granulopoiesis after cytostatic therapy
Development of pneumonia with lung infiltration in patients with log-lasting granulopenia and fever of unknown origin
Reconstitution of cellular immunodeficiency after high-dose chemotherapy with or without stem cell transplantation
Focal lymphadenitis and other mycobacterial diseases
Autoimmune diseases

Table 3. Risk factors of IRIS during ART (4)

Duration of immunodeficiency
Extent of immunodeficiency (nadir of CD4 < 100 cells/ml)
Velocity and (relative) extent of immune reconstitution
Specific pattern of immune reconstitution under ARV
- Immune reconstitution without complete suppression of HIV replication
- High levels of CD8T lymphocytes
- High levels of IL – 6 and soluble IL – 6 receptor
- High levels of soluble CD 30 and soluble CD 26 (dipeptidyl peptidase IV) activity
- High levels of IFN-gamma producing cells
- Increased expression of CCR3 and CCR5 on monocytes and/or granulocytes
- Persisting polyclonal hypergammaglobulinemia
- Development of specific delayed-type of hypersensitivity

Genetic susceptibility
- Distinct HLA haplotypes (HLA B72, Cw 0202, DRB4, HLA A2, B44, HLA A1, B8, DR3 with connection to TNF – alpha polymorphism)
- Polymorphism of cytokine genes
- TNF-alpha (with conjunction with certain HLA haplotype)
- IL-6
- IL-12

Table 4. Other diseases during HIV infection described as having relationships with IRIS after initiation of ART therapy (4)

Mycobacteria (predominantly focal diseases)
- Mycobacterium tuberculosis
- Nontuberculous mycobacteria

Herpes viruses
- Cytomegalovirus (atypical manifestation of eye or skin)
- Herpes simplex virus (recurrent genital herpes)
- Varicella zoster virus (recurrent herpes zoster)
- Ebstein-Barr virus (lymphoproliferation?)
- Kaposi sarcoma herpes virus (Castelman`s disease and Kaposi sarcoma)

Hepatitis viruses
- Hepatitis B virus
- Hepatitis C virus

Protozoal and fungal diseases:
- Toxoplasmosis
- Cryptococcosis
- Microsporidiosis
- Histoplasmosis
- Pnemocystis carini (pneumonitis and granulomata)
- Leismaniosis-pro IRIS (35), contra (36, 37)

PML – Progressive multifocal leucoencephalitis
Cutaneous diseases
- Warts, condylomata accuminata, oral warts
- Eosiniphilic folliculitis

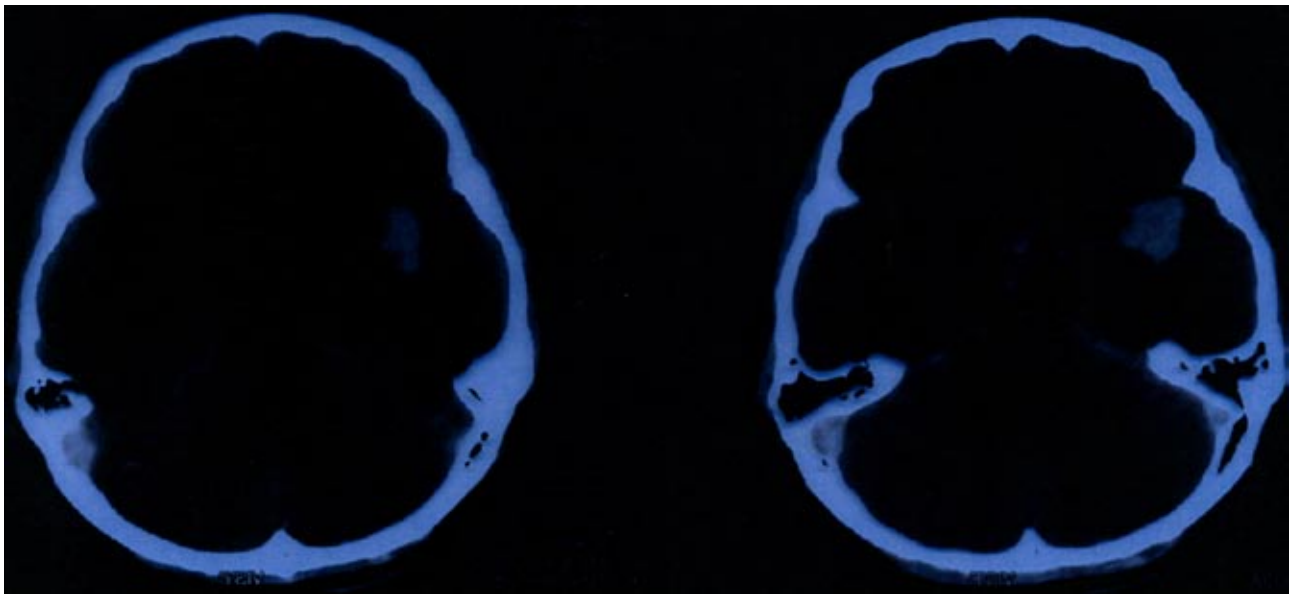
Protozoal or bacterial infections in gastrointestinal tract
- Appendicitis
- Cholecystitis (due to protozoal or mycobacterial coinfection?)
- Splenitis

Guillain-Barre syndrome
Autoimmune diseases
- Systemic Lupus Erythomatosus
- Vasculitis
- Reiter`s Syndrome
- Rheumatoid arthritis
- Polymyositis
- Grave`s disease
- Alopecia universalis

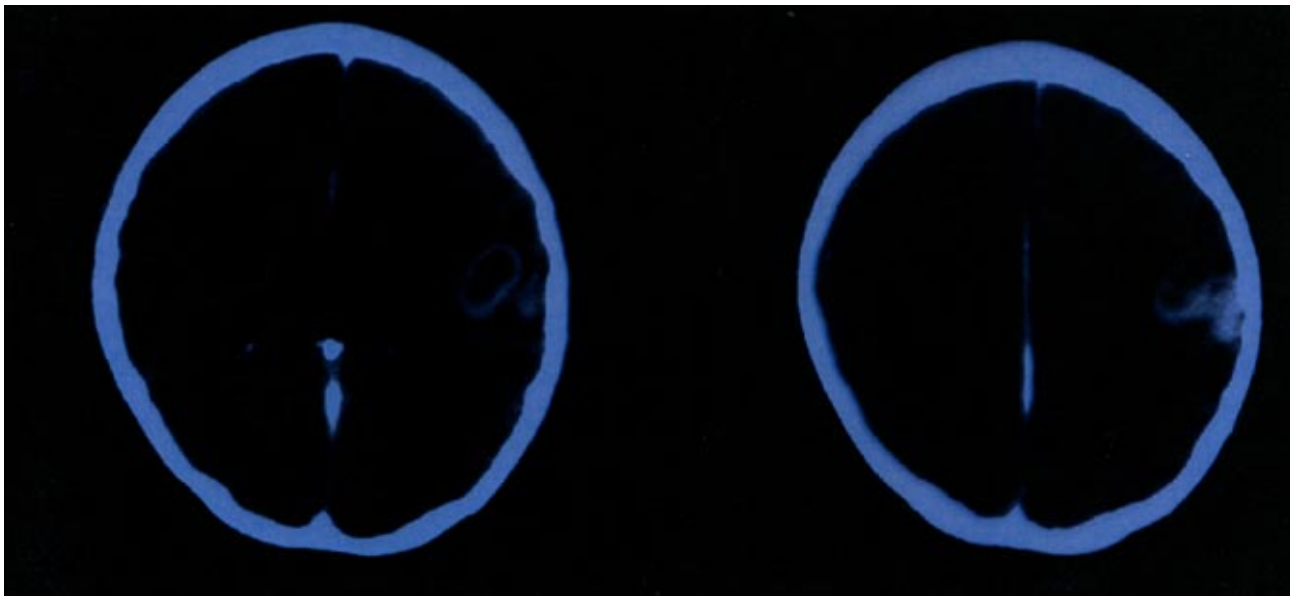
Hyperergic/allergic reaction
- Against tattoos

Neoplasmic diseases
- Kaposi sarcoma
- Atypical immunoproliferation

Other diseases
- Aseptic osteonecrosis
- Gynecomastia
- Sarcoidosis
- Arteriosclerosis



Scan 1. Central Nervous System lesions



Scan 2. Central Nervous System lesions

title

Disseminated nontuberculous mycobacteriosis in a patient with acquired immunodeficiency syndrome – a case report

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summary

The Mycobacterium avium complex (MAC) is the most widespread among the nontuberculous mycobacteriosis and can occur in many natural reservoirs. The infection most commonly occurs by inhalation or drinking water. MAC causes isolated pulmonary disease or disseminated infection, the latter is more frequent in patients with HIV immunosuppression. Systematic symptoms typical for disseminated MAC infection include fever, night sweats, weight loss, diarrhea, abdominal pain, hepatosplenomegaly, lymphadenopathy, respiratory symptoms and abnormal laboratory values. The final diagnosis is established by MAC culture from a sterile site, most often from blood. Preferred regimen of MAC infection includes clarithromycin, azithromycin, rifabutin, ethambutol, levofloxacin, and amikacin for at least 12 months. Chemoprophylaxis with clarithromycin or azithromycin is recommended for patients with HIV with a CD4 count less than 50 cells/mm^3.

We report a case of a 32 year-old Vietnamese male with acquired immunodeficiency syndrome and disseminated MAC infection resistant for majority of antimycobacterial agents.

key words

disseminated MAC infection, HIV infection, antimycobacterial treatment, chemoprophylaxis, resistance

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Background

MAC „Mycobacterium avium complex" is an opportunistic infection caused by two similar bacteria: Mycobacterium avium and Mycobacterium intracellulare. MAC can be recovered from many natural reservoirs such as water, soil, food, animals as well as hot water pipe systems, including hospital water supplies. The major MAC infection risk factors are age, sex, immunosuppression, pulmonary diseases as well as cigarettes and alcohol abuse. There are two main modes of MAC transmission: inhalation through the respiratory tract and ingestion via the gastrointestinal tract. Probability of human-to-human transmission is minimal. Pathogenesis of this disease is poorly understood. MAC can infect macrophages and spread to the local lymph nodes. However, in immunocompromised hosts, they are subsequently spread via the hematogenous route to the liver, spleen and other organs. MAC infection usually presents in pulmonary forms in immunocompetent hosts, disseminated MAC (DMAC) in individuals with advanced AIDS or lymphadenitis in children [1, 2].

In this paper, we report a case of a 32 year-old Vietnamese male with acquired immunodeficiency syndrome and disseminated MAC infection resistant for majority of antimycobacterial agents. The aim of our case study is to stress wide MAC prevalence among immigirants, especially from Asia as well as the crucial role of its prophylaxis and early treatment.

Case report

A 32 year-old Vietnamese male, staying in Poland for 10 years, a cook, married, and a father of 2 children, was admitted to our Department in March 2007, after a 3-day hospitalization in the Internal Diseases Department where he had been recognized as a carrier of the human immunodeficiency virus (positive anti-HIV ELISA). He had a 3-month history of general weakness, weight loss, high fever, moderate epigastric pain and chronic diarrhea. Six months before hospitalization he traveled to Vietnam. His history of IVDU was unclear however he had some hazardous sexual intercourse.

Laboratory tests performed in the Internal Diseases Department showed anaemia (HGB-7.2 g%, RBC-2.7x10^6, HCT-21.6%), leucopenia (WBC-2.7x10^3), hypoalbuminaemia, an elevation of aminotransferases (ALT-73U/L; AST-101U/L) and γ-glutamyl transpeptidase to 442 U/L, serum alkaline phosphatase to 865 U/L and lactate dehydrogenase to 439 U/L. Serology was negative for hepatitis B surface antigen (HbsAg) and antibodies to hepatitis C (anti HCV). Chest X-ray film showed pulmonary congestion and left heart enlargement. Abdominal ultrasonography discovered an enlarged liver and spleen without focal lesions. Abdominal CT scan additionally revealed pulmonary inflammatory changes, pleural and peritoneal effusion and para-aortic lymphadenopathy. In an electrocardiogram isolated negative T wave in lead V2 and V3 was observed. Due to the aggravation of general condition and circulatory insufficiency, intravenous antibiotic therapy (cephtriaxone, trimethoprim/ sulfamethoxazole) and dopamine infusion was initiated.

The physical examination during admission to our Department showed clinical signs of shock: fast, weak pulse (120 per minute), low blood pressure (RR 80/60 mmHg), pallor, sweatiness and anxiousness. In abdominal examination, epigastric tenderness and an enlarged, palpable, tender liver and spleen were observed. Inguinal and axillary lymph nodes were moderately enlarged.

Control chest X-ray and ultrasonography performed on the day of admission showed progressive pulmonary inflammation, enlargement of the cardiac silhouette and increasing pleural effusion (Figure 1). Control electrocardiogram showed new incomplete right bundle branch block (RBBB). An echocardiogram revealed a pericardial effusion and left heart failure (EF 35%). Tuberculin skin reaction was negative. Bacterial and fungal cultures of sputum yielded Streptococcus haemoliticus and Candida crusei. Microscopical sputum examination revealed acid-fast bacilli. Antibacterial (ceftazidime, trimethoprim/sulfamethoxazole and vancomycine), antifungal (amphotericin B) and antimycobacterial (rifampicin, isoniazid, ethambutol, pirazinamide) and beta blocker therapy was initiated.

Early HIV-infection parameters were: CD4 cell count – 19/mm^3, CD8 cell count – 126 mm^3, CD4/CD8 ratio – 0.15 and viral load – 1 310 copies/ml. HIV subtype was identified as a CRF01-AE. HIV-1 Genotyping Test yielded primary resistance to didanosine (ddI), delavirdine (DLV) and tipranavir boosted ritonavir (TPV/r).

On the 5th in-hospital day, antiretroviral therapy with nevirapine (NVP), tenofovir (TDF) and emtricitabine (FTC) was introduced. Despite HAART and antimycobacterial treatment, patient did not show clinical improvement. Moreover, new focal lesions in the liver and spleen were observed in abdominal ultrasonography. About ten days later, microscopical examination of blood showed acid-fast bacilli. He was diagnosed as possible disseminated nontuberculous mycobacteriosis and treated with clarithromycine, ofloxacine and ethambutol. His clinical symptoms improved and the sputum and blood microscopical examination showed no acid-fast bacilli.

Three weeks later he was admitted for the second time to our Department because of fever, cough, jaundice, progression of cahexia, epigastrical pain and splenomegaly. Chest X-ray still showed enlargement of the cardiac silhouette (Figure 2). All cultures converted to negative for acid-fast bacilli but bacterial and fungal cultures of sputum yielded Sthapylococcus aureus, Candida crusei and Candida glabrata. At this time, his CD4 cell count was 0/mm^3. Administration of several kinds of antibiotics, antifungal, antimycobacterial and antiviral agents did not relieve the symptoms. On the 4th day the patient had developed a cardiopulmonary failure and died few hours later.

Retrospectively the acid-fast bacilli were identified as Mycobacterium avium complex (MAC) resistant for rifampicin, isoniazid and ethambutol. His final diagnosis was disseminated MAC infection, acute cardiopulmonary failure, and staphylococcal sepsis suspicion.

Discussion

Disseminated MAC infection (DMAC) is the most common bacterial opportunistic infection among HIV(+) patients. It occurs in 20-40% of patients with a CD4 count below 100 cells per mm^3 without HAART and MAC profilaxis but only in 2% with appropriate therapy [3].

Our patient was in severe immunosuppression with CD4 count about 19 cells/mm^3 and presented systematic symptoms typical for DMAC including fever, night sweats, weight loss, diarrhea, abdominal pain, hepatosplenomegaly, lymphadenopathy and respiratory symptoms and abnormal laboratory values such as raised serum alkaline phosphatase (865 U/L), lactate dehydrogenase (439 U/L)

and anaemia. These symptoms are also observed in Mycobacterium tuberculosis infection as well as the presence of acid-fast bacilli in sputum examination. The final MAC infection diagnosis is established by a MAC culture from a sterile site, most often from blood. Moreover liver, bone marrow or lymph nodes biopsy is sometimes required. In our patient's blood, microscopical examination showed acid-fast bacilli after ten days of hospitalization. The optimal HAART and antimycobacterial therapy was introduced. His regimen consisted of nevirapine (NVP), tenofovir (TDF) and emtricitabine (FTC) as well as rifampicin, isoniazid, ethambutol, pirazinamide and than clarithromycine, ofloxacine and ethambutol.

According to guidelines, preferred regimen of MAC infection including clarithromycin, azithromycin, rifabutin, ethambutol, levofloxacin, and amikacin for at least 12 months is probably the most active. Second-line antituberculosis drugs are also occasionally used.

Chemoprophylaxis with clarithromycin or azithromycin is recommended for patients with HIV with a CD4 count less than 50 cells/mm^3 [4].

Conclusion

In conclusion, the diagnosis of MAC infection should be considered in HIV (+) patients with CD4 count below 50 cells /mm^3 . We suggest routine sputum and blood analysis towards Mycobacterium tuberculosis as well as MAC infections for all HIV (+) immigrants. Early prophylaxis and therapy can reduce the significant morbidity and mortality associated with disseminated MAC. On the other hand, we would like to underline the relationship between the clinical efficacy of treatment and drug-sensitivity testing of MAC isolates for antituberculous drugs [5]**.** Moreover, all MAC infected individuals should be closely monitored because some life-threatening complications have been reported during nontuberculous mycobacteriosis [6].

References

1. Watanabe KMF, Kasahara K. Characteristics of pulmonary Mycobacterium avium intracellulare complex (MAC) infection in comparison with those tuberculosis. Respir Med 2003; 97: 654-9.
2. Wagner D, Young LS. Nontuberculous mycobacterial infections: a clinical review. Infection 2004; 32,:257-70.
3. Karakousis PC, Moore RD, Chaisson RE. Mycobacterium avium complex in patients with HIV infection in the era of highly active antiretroviral therapy. Lancet Infect Dis. 2004; 4: 557-65.
4. Lange CG, Woolley IJ, Brodt RH. Disseminated mycobacterium avium-intracellulare complex (MAC) infection in the era of effective antiretroviral therapy: is prophylaxis still indicated? Drugs 2004; 64: 679-92.
5. Kobashi Y, Yoshida K, Miyashita N, Niki Y, Oka M. Relationship between clinical efficacy of treatment of pulmonary Mycobacterium avium complex disease and drug-sensitivity testing of Mycobacterium avium complex isolates. J Infect Chemother. 2006; 12: 195-202.
6. Huh JJ, Panther LA,. Mycobacterium avium complex peritonitis in an AIDS patient. Scand J Infect Dis. 2001; 33: 936-8.

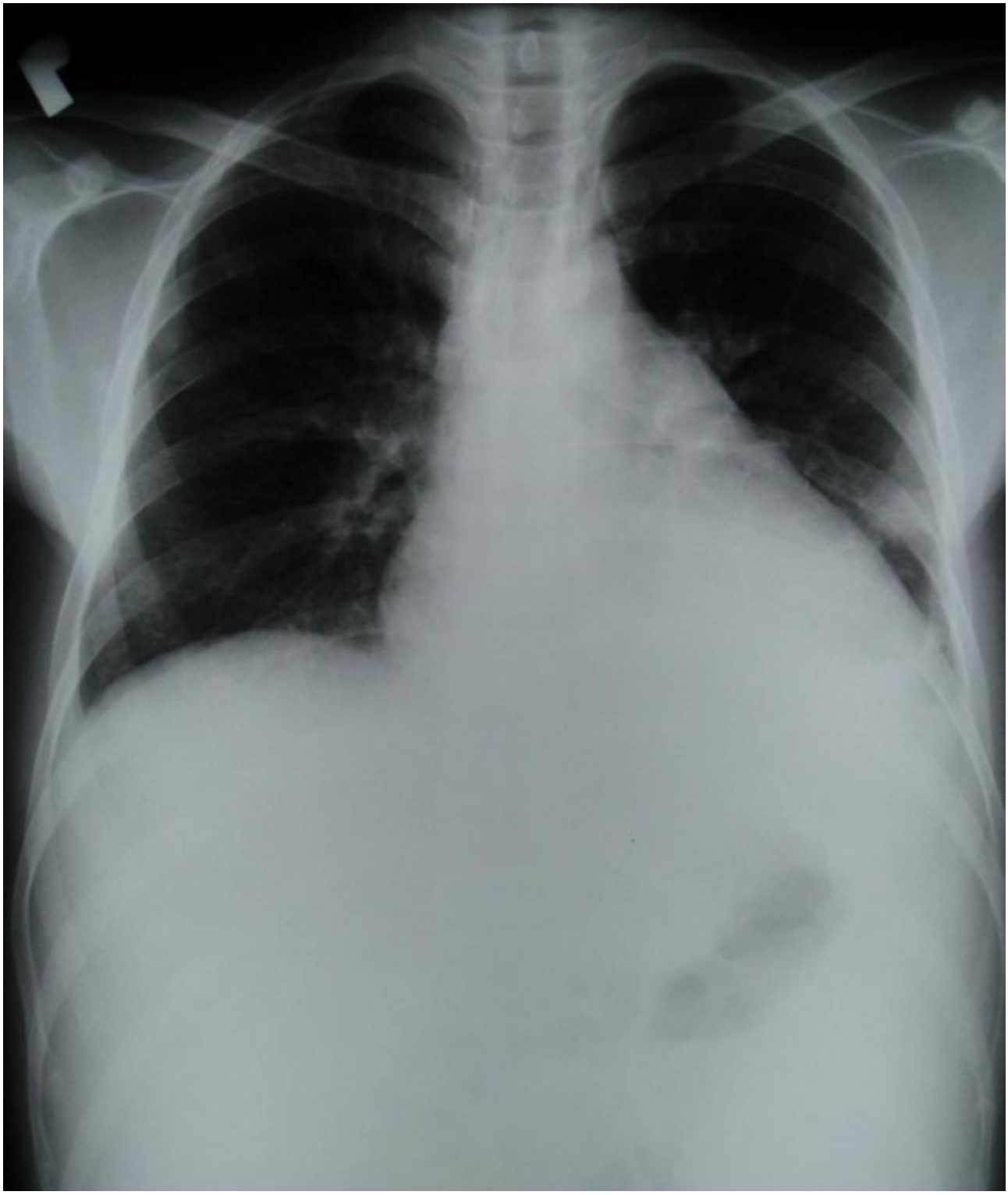

Figure 1. Patient's chest X-ray on admission to our Department (29.03.2007)

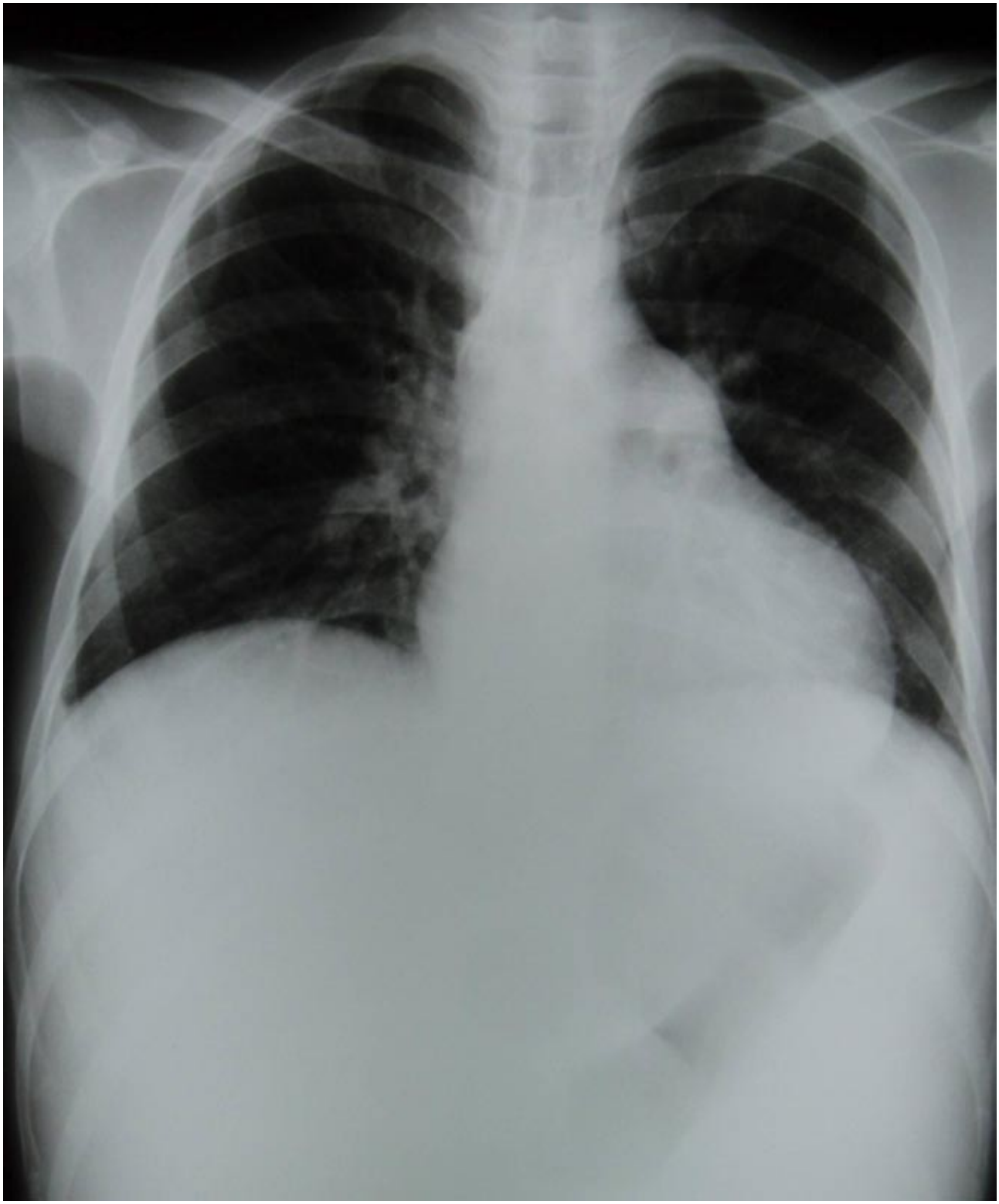

Figure 2. Patient's chest X-ray during the second hospitalization in our Department (16.06.2007)

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